COMMERCIAL ORGANIC ANALYSIS

A TREATISE ON THE

PROPERTIES, PROXIMATE ANALYTICAL EXAMINATION, AND MODES OF ASSAYING THE VARIOUS ORGANIC CHEMICALS AND PRODUCTS EMPLOYED IN THE ARTS, MANUFACTURES, MEDICINE, &c.;

WITH CONCISE METHODS FOR

THE DETECTION AND DETERMINATION OF THEIR IMPURITIES, ADULTERATIONS, AND PRODUCTS OF DECOMPOSITION

BY

ALFRED H. ALLEN, F.I.C., F.C.S.

PAST PRESIDENT OF THE SOCIETY OF PUBLIC ANALYSTS,
PUBLIC ANALYST FOR THE WEST RIDING OF YORKSHIRE, THE NORTHERN DIVISION OF DERBYSHIRE, THE COUNTY-BOROUGH OF SHEFFIELD, &c.

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VOLUME III—PART II

AMINES AND AMMONIUM BASES, HYDRAZINES, BASES FROM TAR, VEGETABLE ALKALOIDS.

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VOLUME III. PART I., Price 14*s.*, contains:—

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PREFACE TO VOLUME III.—PART II.

IT is ten years since the publication of the last edition of that part of COMMERCIAL ORGANIC ANALYSIS which treated of Alkaloids and Tar Bases. These subjects then occupied about 120 pages. In the edition now issued 570 pages have already been printed, and I feel reluctantly compelled to publish the subject-matter now ready as PART II. of VOLUME III., leaving the sections on the less important ALKALOIDS and the chapters on ANIMAL BASES, CYANOGEN COMPOUNDS, PROTEIDS, &c., to be issued separately as PART III.

In PART II., now published, I have endeavoured to describe fully and accurately such of the Organic Bases as have any practical interest, and to give reliable information as to their sources. The AMINES, HYDRAZINES, and PYRIDINE and its Derivatives are now considered for the first time. The ANTIPYRETICS, and other synthetical remedies with which modern Chemistry has enriched medicine, are described fully, in cases where they fall appropriately within the scope of the present Volume; and I believe the sections on Antipyrine, Antifebrin, Phenacetin, Thalline, &c., contain a resumé of all published information on their respective subjects. In the Chapter on VEGETABLE ALKALOIDS I have spared no pains to render the more important articles as complete and trustworthy as possible, and in this endeavour have received most

valuable assistance from Mr W. Chattaway, Mr A. J. Cownley, Mr R. A. Cripps, Mr D. B. Dott, Mr A. W. Gerrard, Mr O. Hehner, Dr B. H. Paul, Mr M. J. Sheridan, Dr C. R. Alder Wright, and Mr R. Wright, who have kindly perused and corrected some of the more important sections. When it is borne in mind that the article on Aconite Bases occupies 44 pages, that on Atropine and its Allies 27, Coca Alkaloids 23, Opium Alkaloids 67, Cinchona Alkaloids 79, and Tea and Coffee 27 pages each, it is evident that these gentlemen had no light task.

I have also to acknowledge the zealous assistance of Mr G. E. Scott Smith, Mr C. M. Caines, Mr G. S. A. Caines, and other workers in my laboratory, in researches on the Assay of Aconite Bases, the Determination of Caffeine, and much similar original experimental work, the results of which will be found duly recorded.

In the sections on Tea, Coffee, and Cocoa, which conclude the Volume and together occupy 73 pages, I have incorporated nearly every item of trustworthy information of a chemical nature within my knowledge, and I believe these articles will be found of service by many besides professional chemists.

Part III., completing the work, will be published as soon as possible, and will, I hope, be followed at no distant date by a New Edition of the earlier Volumes.

ALFRED H. ALLEN.

101, Leadenhall Street,
London, E.C., 1st *October* 1892.

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AMINES AND AMMONIUM BASES.

Wurtz, in 1848, pointed out that one of the hydrogen atoms of ammonia, H_3N, could be replaced by ethyl, C_2H_5, and shortly afterwards A. W. Hofmann proved that the substitution by ethyl and other alkyl radicals could be extended to the second and third atoms of hydrogen, the new bodies thus produced being powerfully alkaline and in other respects closely resembling ammonia itself. Hofmann called these new bases amines, and proved them to be the simplest members of a numerous class of synthetically producible compounds. He classified them as primary, secondary, and tertiary amines, according as one, two, or all three of the hydrogen atoms of the ammonia-molecule were replaced by alcoholic or alkyl radicals. As these atoms of hydrogen may be, and very often are, replaced by two or more different organic radicals, mixed amines exist, and are capable of numerous metameric modifications. Thus a base having the empirical formula $C_5H_{13}N$ may have any one of the five following constitutions :—

1. Amyl-amine, ... $\left.\begin{matrix} C_5H_{11} \\ H \\ H \end{matrix}\right\} N$

2. Butyl-methyl-amine, ... $\left.\begin{matrix} C_4H_9 \\ CH_3 \\ H \end{matrix}\right\} N$

3. Propyl-ethyl-amine, ... $\left.\begin{matrix} C_3H_7 \\ C_2H_5 \\ H \end{matrix}\right\} N$

4. Propyl-dimethyl-amine, ... $\left.\begin{matrix} C_3H_7 \\ CH_3 \\ CH_3 \end{matrix}\right\} N$

5. Diethyl-methyl-amine, ... $\left.\begin{matrix} C_2H_5 \\ C_2H_5 \\ CH_3 \end{matrix}\right\} N$

Of these metameric bases,[1] the first only is a primary monamine; the second and third are secondary amines; and the fourth and fifth tertiary bases. They could be distinguished by their behaviour with ethyl iodide, nitrous acid, and the other reactions described on page 4 *et seq.*

The hydrogen of ammonia may also be replaced by an acid radical, such as acetyl or benzoyl, when the resultant compound no longer possesses basic properties, and is termed an amide (*e.g.*, acetamide, $C_2H_3O.NH_2$). Mixed compounds also exist, such as

$$\left.\begin{array}{c} CH_3 \\ C_2H_3O \\ H \end{array}\right\} N;$$

which may be called either methyl-acetamide or acetyl-methylamine. Bases are also known which are derived from the replacement of certain of the atoms of hydrogen in two, three, and even four associated molecules of ammonia, the products being called respectively diamines, triamines, and tetramines, which closely resemble the monamines in their general characters. The following are examples of such bases:—

MONAMINES—

Phenylamine (Aniline).

$$\left.\begin{array}{c} (C_6H_5) \\ H \\ H \end{array}\right\} N$$

Diethylamine.

$$\left.\begin{array}{c} (C_2H_5) \\ C_2H_5 \\ H \end{array}\right\} N$$

Trimethylamine.

$$\left.\begin{array}{c} (CH_3) \\ (CH_3) \\ (CH_3) \end{array}\right\} N$$

DIAMINES—

Phenylene-diamine.

$$\left.\begin{array}{c} H_2 \\ (C_6H_4)'' \\ H_2 \end{array}\right\} N_2$$

Diethylene-diamine.

$$\left.\begin{array}{c} H_2 \\ (C_2H_4)'' \\ (C_2H_4)'' \end{array}\right\} N_2$$

Triethylene-diamine.

$$\left.\begin{array}{c} (C_2H_4)'' \\ (C_2H_4)'' \\ (C_2H_4)'' \end{array}\right\} N_2$$

TRIAMINES—

Diethylene-triamine.

$$\left.\begin{array}{c} H_5 \\ (C_2H_4)'' \\ (C_2H_4)'' \end{array}\right\} N_3$$

Triethylene-triamine.

$$\left.\begin{array}{c} H_3 \\ (C_2H_4)'' \\ (C_2H_4)'' \\ (C_2H_4)'' \end{array}\right\} N_3$$

TETRAMINES—

Triethylene-tetramine.

$$\left.\begin{array}{c} H_6 \\ (C_2H_4)_3'' \end{array}\right\} N_4$$

[1] It is evident that the formulæ in the text do not exhaust all possible modifications of the base $C_5H_{13}N$, as they do not take into account the various isomeric modifications of which propyl, butyl, and amyl are susceptible.

Interesting bases are also obtainable by the substitution of organic radicals for the hydrogen atoms of H_3P, H_3As, and H_3Sb.

The majority of the known bodies of the amine class are synthetical compounds of great scientific but little practical interest. Some few amines have been found to exist naturally in plants (*e.g.*, trimethylamine, conine), and others are met with in animal fluids (*e.g.*, urea), or the products of the decomposition of animal matters (leucine, glycocine). The tar-bases may be regarded as belonging to the amine class, aniline and toluidine being primary, and pyridine and quinoline tertiary monamines. Piperidine, conine, and sarcocine are examples of secondary monamines; while urea and diamidobenzene may be regarded as diamines, and biuret and guanidine as triamines. Choline and neurine are related to the tetra-alkyl-ammonium bases. The monamines may be advantageously considered at the present stage, but the majority of the amine bases will be more conveniently described in other chapters.

MONAMINES.

These bases are derived from one molecule of ammonia by the substitution of one or more of the hydrogen atoms by an equivalent number of alkyl radicals. The first body obtained of this class was ethylamine, $C_2H_5.NH_2$, prepared by Wurtz in 1848 by distilling ethyl cyanurate with caustic potash. Methylamine, $CH_3.NH_2$, was obtained by the same chemist in the following year, by the distillation of methyl isocyanate (acetonitrile) with caustic alkali :—$2KOH + CH_3.N.CO = K_2CO_3 + CH_3.NH_2$.

Hofmann obtained the monamines by the reaction of an alkyl iodide on an alcoholic solution of ammonia. The reaction is not a simple one, all three monamines being formed together with a tetra-alkylated ammonium base. Thus, when ethyl iodide is heated with alcoholic ammonia to 100° in a sealed tube, there are obtained :—

Hydriodide of ammonia, . . .	$H_3N,HI = H_4NI$
„ monoethylamine, .	$(C_2H_5)H_2N,HI = (C_2H_5)H_3NI$
„ diethylamine, .	$(C_2H_5)_2HN,HI = (C_2H_5)_2H_2NI$
„ triethylamine, .	$(C_2H_5)_3N,HI = (C_2H_5)_3HNI$
Iodide of tetra-ethyl-ammonium,.	$(C_2H_5)_3N,C_2H_5I = (C_2H_5)_4NI$

Similar products result when bromide or chloride of ethyl is substituted for the iodide, except as to the relative proportions of the amines obtained. Thus chloride of ethyl produces almost exclusively EtH_3NCl, with small quantities of Et_2H_2NCl and

Et_4NCl; ethyl bromide gives chiefly EtH_3NBr, with very appreciable quantities of Et_2H_2NBr and Et_3HNBr, but very little Et_4NBr; while ethyl iodide produces EtH_3NI, Et_2H_2NI, and Et_3HNI in about equal proportions, as well as very appreciable quantities of Et_4NI (Groves, *Jour. Chem. Soc.*, xiii. 331).

A similar series of products is obtained by heating iodide, bromide, or nitrate of methyl with a solution of ammonia in methyl alcohol. When the methyl nitrate and ammonia solution are used in equivalent proportions for the reaction—$MeNO_3 + H_3N = MeH_2N,HNO_3$, monomethylamine is the chief product, though more or less of each of the more highly substituted products is also formed. With excess of methyl nitrate, the nitrate of tetramethyl-ammonium, $Me_4N.NO_3$, is produced in large excess, and the same quaternary compound is formed if methyl bromide or iodide be substituted for the nitrate.

The complex nature of the products obtained by treating alkyl iodides, &c., with alcoholic ammonia is due to the tendency of the amines first produced to react on the remaining portions of the alkyl iodide or other salt to form ammonium iodide and more highly substituted amines. Thus:—

$$H_3N + C_2H_5I = (C_2H_5)H_3NI$$
$$(C_2H_5)H_2N + C_2H_5I = (C_2H_5)H_2NI$$
$$(C_2H_5)_2HN + C_2H_5I = (C_2H_5)_3HNI$$
$$(C_2H_5)_3N + C_2H_5I = (C_2H_5)_4NI$$

The hydriodides of the amines similarly react with alkyl iodides in presence of ammonia to form ammonium iodide and more highly substituted amines.

From these reactions it follows that the hydriodide of diethylamine, for instance, may be obtained by heating the bromide or iodide of ethyl with a calculated amount of mono-ethylamine in a sealed tube. A great variety of mixed amines may be obtained by precisely similar means.

Distinction and Separation of Primary, Secondary, and Tertiary Monamines.

a. If an amine be heated to 100°, under pressure, with an excess of alkyl iodide, a quaternary iodide will at length be formed, and the problem whether the original base was a primary, secondary, or tertiary amine will be solved by comparing the composition of the ultimate product with that of the original base or its hydriodide. Thus, if methyl iodide has been the alkylising agent employed, the iodide of the compound ammonium ultimately obtained will differ from the hydriodide of the original

base by $3CH_2$, if the amine was primary; by $2CH_2$, if secondary; and by CH_2, if tertiary.

b. The following is an outline of the method devised by A. W. Hofmann for the separation of the mixed amines resulting from heating ethyl iodide with alcoholic ammonia:—The product of the reaction is filtered from ammonium iodide, which is nearly insoluble in the alcoholic liquid, and is evaporated to dryness to get rid of excess of alcohol, free ammonia, and unchanged alkyl iodide. The residue is then distilled with caustic potash, when the hydriodides of the amines are decomposed, the bases volatilising, while the iodide of the tetra-alkylated ammonium base remains in the retort unchanged by, and insoluble in, the strong potash solution. The mixture of amines is conducted over caustic lime, and then condensed by passage through a well-cooled tube. The bases are then treated in a flask with one and half times their weight of ethyl oxalate (previously dried over calcium chloride), which is added gradually through a tapped funnel. This has no action on triethylamine or other tertiary bases, but converts diethylamine into liquid ethyl diethyl-oxamate, and mono-ethylamine into solid diethyl-oxamide,[1] according to the following equations:—

$$1.\ (C_2H_5)_2C_2O_4 + 2(C_2H_5)NH_2 = C_2O_2\begin{cases}NH(C_2H_5)\\NH(C_2H_5)\end{cases} + 2(C_2H_5)OH$$

Ethyl oxalate. Ethylamine. Diethyl-oxamide. Alcohol.

$$2.\ (C_2H_5)_2C_2O_4 + (C_2H_5)_2NH = C_2O_2\begin{cases}O.C_2H_5\\N(C_2H_5)_2\end{cases} + (C_2H_5)OH$$

Ethyl oxalate. Diethylamine. Ethyl Diethyl-oxamate. Alcohol.

The liquid gets very hot, but for the completion of the reaction the mixture should be heated to 100° for several days in a closed vessel. The triethylamine, which has taken no part in the reaction, is then distilled off on the water-bath. The residue is well cooled, and the solid oxamide separated from the liquid oxamate by pressure.[2] On subsequent distillation with caustic potash,

[1] Diethyloxamide may also be separated from the ethyl diethyloxamate by cold water, in which the former dissolves easily, the latter very sparingly. If hot water be used, the separation is more perfect and the residual oxamate quite pure; but some of it suffers hydrolysis and goes into solution as diethyloxamic acid.

[2] Some ethyl monoethyloxamate, $C_2O_2\begin{cases}O.C_2H_5\\NH.C_2H_5\end{cases}$, is always formed from the primary amines in this reaction.

these compounds yield the primary and secondary amines respectively:—

1. $C_2O_2(NH.C_2H_5)_2+2H.(OK)=C_2O_2(OK)_2+2H(NH.C_2H_5)$

2. $C_2O_2\left\{\begin{matrix}O(C_2H_5)\\N(C_2H_5)_2\end{matrix}\right.+2H.(OK)=C_2O_2(OK)_2+H.N(C_2H_5)_2+H.O(C_2H_5)$

The foregoing process is available, with certain modifications in detail, for the separation of the amines of methyl and other homologues of ethyl, and, in fact, is of general application for the separation of primary, secondary, and tertiary amines; the first class forming oxamides, the second oxamic ethers, and the third being unacted on by ethyl oxamate.

An important modification in the foregoing method has been made by Duvillier and Buisine (*Ann. Chim. Phys.*, [5], xxiii. 289), who operate on an aqueous solution of the bases. Under these conditions, the primary amines are converted by ethyl oxalate into insoluble or sparingly soluble oxamides, while the secondary and tertiary bases are unchanged, or at any rate remain wholly in solution. After separating the oxamides by filtration, the mother-liquor[1] [is boiled for some time, which causes the hydrolysis of the ethyl diethyloxamate with formation of diethyloxamic acid, $(C_2H_5)_2N.C_2O_2.OH$, and the further change of this into the acid oxalate of diethylamine, $(C_2H_5)_2HN.H_2C_2O_4$.[1] This salt separates on cooling, and yields the free base on distillation with alkali. The filtrate] is distilled with potash, the bases dried by caustic potash, and dissolved in absolute alcohol. On adding ethyl oxalate to this solution the secondary amines are converted into oxamic ethers, while any remaining primary amines are converted into the corresponding oxamides. After allowing the mixture to stand for twenty-four hours to complete the reaction, the alcohol and unchanged *tertiary bases* are distilled off on the water-bath. The oxamates remaining in the retort may be converted into calcium salts by treatment with milk of lime, or the *secondary bases* at once liberated and recovered by distillation with caustic potash.[2]

[1] The treatment described in the brackets is optional, and chiefly of advantage in the separation of ethylamines.

[2] The conversion into calcium salts is especially suitable for the treatment of the ethylamines. The precipitated calcium diethyloxamate and monoethyloxamate are filtered off, and the filtrate treated with alcohol, which precipitates the remainder of the calcium salts. The precipitates are treated with boiling water, when the monoethyloxamate dissolves, and is deposited again on cooling in large crystals, which on distillation with potash yield *ethylamine.* On concentrating and cooling the mother-liquors, calcium diethyloxamate separates. It is recrystallised from alcohol, washed with ether to remove any adhering oxamide, and distilled with potash, when it yields pure *diethylamine.*

Duvillier and Buisine have applied this method to the analysis of the complex mixture of amines present in commercial trimethylamine from *vinasses* (page 13). A. Müller (*Bull. Soc. Chim.*, xlii. 202; *Jour. Chem. Soc.*, xlviii. 501) has described a method for the separation of amines based on much the same principle.

The primary, secondary, and tertiary monamines may also be distinguished by the following reactions :—

c. If a primary monamine be boiled with alcoholic potash and chloroform, the characteristic and highly disagreeable odour of the corresponding carbamine or isonitrile is evolved, according to the reaction :—$MeNH_2 + CHCl_3 + 3KHO = MeNC + 3H_2O + 3KCl$.

d. If a primary fatty monamine be dissolved in a mixture of equal measures of alcohol and carbon disulphide, and the liquid then boiled down to one-half, a thiocarbamate will be formed thus :—$2MeNH_2 + CS_2 = MeNH.CS.S.NMeH_3$.

If the resultant liquid be boiled with a solution of mercuric or ferric chloride, a pungent odour of mustard oil will be produced. owing to the formation of an alkyl iso-thiocyanate :[1]—

$$MeNH.CS.S.NMeH_3 + HgCl_2 = HgS + MeNCS + NMeH_3Cl.$$

e. *Nitrous acid* converts *primary fatty monamines* into the corresponding alcohols :—$MeH_2N + NO.OH = Me.OH + OH_2 + N_2$.

Aromatic primary amines (*e.g.*, aniline) are converted by nitrous acid into diazo-compounds :—$PhNH_2 + NO.OH = Ph.N{:}N.OH + H_2O$.

Secondary amines, whether fatty or aromatic, are converted by nitrous acid into nitrosamines, thus :—$Me_2NH + NO.OH = Me_2N.NO + H_2O$. The nitrosamines are yellow liquids, of neutral character and aromatic odour, volatile without decomposition in a current of steam. Weak reducing agents convert them into hydrazines (page 27); but by more powerful hydrogenising agents, or by warming with alcohol and hydrochloric acid, they are reconverted into the original secondary amines.

Nitrous acid has no action on *tertiary fatty amines*. It converts most *tertiary aromatic amines* into nitroso-derivatives which still possess basic properties.

In practice, the action of nitrous acid on the amines is best effected by distilling their hydrochlorides with a strong solution of potassium or sodium nitrite. If a mixture of the hydrochlorides of the three methylamines be thus treated, the *monomethylamine* is destroyed (with formation of methyl alcohol, which will be found

[1] In the case of aromatic primary amines, the product is usually a thio-urea, which requires to be treated with phosphoric pentoxide to obtain the iso-thiocyanate.

in the distillate), *dimethylamine* is converted into dimethyl-nitrosamine, which distils,[1] while the hydrochloride of *tri-methylamine* remains in the retort (mixed with excess of the metallic nitrite), and on distilling it with caustic alkali the free base can be obtained.

f. Both *primary* and *secondary monamines* react with aldehydes to form indifferent bodies. The reaction between œnanthol and mono- and di-methylamine respectively is as follows:—

$$H_2.N.CH_3 + C_6H_{13}.CHO = H_2O + C_6H_{13}.CH.NCH_3 \text{; and}$$

$$2HN(CH_3)_2 + C_6H_{13}.CHO = H_2O + C_6H_{13}.CH[N(CH_3)_2]_2.$$

This reaction has been utilised by Schiff (*Annalen*, clix., 158) for the volumetric assay of amines. The base is dissolved in benzene, fused calcium chloride added, and then a standard solution of œnanthol in benzene dropped in from a burette as long as water continues to separate. Each addition of the œnanthol solution produces a turbidity from separation of water, but this is absorbed by the calcium chloride on gentle agitation. As a primary amine reacts with twice as much œnanthol as the corresponding secondary amine, the proportions of the two in a mixture can be estimated from the result of the titration, provided the mean combining weight of the mixture be known, or ascertained in a separate experiment by titration with standard acid.

g. The acid ferrocyanides of the *tertiary amines* are remarkably insoluble in water. They are precipitated on adding potassium ferrocyanide to the solutions of the amines acidulated with hydrochloric acid. The bases can be recovered from their ferro-cyanides by treating the precipitate with solution of cupric sulphate, filtering, and removing the sulphuric acid and excess of copper from the filtrate by baryta-water.

GENERIC CHARACTERS OF MONAMINES.

The monamines, as a class, are readily volatile liquids, of lower specific gravity than water. Their boiling-points rise with the number of carbon atoms in the molecule. They are inflammable, burning with a yellow flame; and the lower members dissolve with great facility in water, forming strongly alkaline liquids of an ammoniacal odour. From their solutions, ethylamine and the higher homologues can be separated by saturating the liquid with caustic potash. By boiling the aqueous solutions of the free

[1] On separating the nitrosamine, which forms a yellow oil, from the aqueous distillate, treating it with aqueous hydrochloric acid, and then passing hydrochloric acid gas till the liquid is homogeneous, the hydrochloride of the secondary amine is formed, and may be obtained by evaporation of the solution.

bases, or of their salts after adding excess of lime or fixed caustic alkali, the monamines can be completely volatilised, and condensed again in water or acid, and titrated in the same manner as ammonia. The monamines are all powerful bases, closely resembling ammonia in their general characters. They form crystallisable salts, and yield chloroplatinates, chloraurates, and alums, exactly similar in characters and constitution to the corresponding compounds of ammonia. The monamines precipitate magnesium salts, but the precipitated magnesium hydroxide dissolves in the amine hydrochloride, forming a double salt from the solution of which phosphate of sodium precipitates an amino-magnesium phosphate. The amines thus behave exactly in the same manner as ammonia.

The only amines (not described in other chapters) requiring detailed consideration are the primary, secondary, and tertiary monamines of methyl and ethyl. These bodies are typical of the amines generally, and most of the statements made respecting them would be true of all the bodies of the class. Their aqueous solutions dissolve silver chloride, and behave in much the same manner as ammonia with metallic salts; but there are some interesting differences, as shown in the table on next page, from which it will be seen that certain of the precipitates which are soluble in excess of ammonia are undissolved by the amines, and *vice versa*.[1]

In all cases a solution of aluminium phosphate in hydrochloric acid behaves similarly to a solution of aluminium chloride (Taylor).

Methylamine. Monomethylamine.

$$CH_5N = \left.\begin{matrix} CH_3 \\ H \\ H \end{matrix}\right\} N.$$

Methylamine exists ready-formed in *Mercurialis annua* and *M. perennis*, and, as obtained (in an impure state) from these plants, was formerly known as mercurialine. It also exists in herring-brine, coal-tar, bone-oil, and the products of the distillation of wood,[2] beetroot molasses (*vinasses*), and certain alkaloids

[1] The author is indebted to Leo Taylor for repeating and enlarging on the experiments of Vincent, on whose observations the table is chiefly founded. Several blanks in the observations of Vincent have been filled by Taylor.

[2] The presence of the amines of methyl in pyroligneous acid and wood spirit is probably due to the reaction of acetone and ammonia:—$C_3H_6O + NH_3 = C_2H_4O + (CH_3).NH_2$. This equation has been experimentally verified.

Metallic Salt.	*Ammonia.* H_3N	*Ethylamine.* $(C_2H_5)H_2N$	*Methylamine.* $(CH_3)H_2N$	*Dimethylamine.* $(CH_3)_2HN$	*Trimethylamine.* $(CH_3)_3N$
Aluminium.	Insoluble (nearly).	Soluble.	Soluble.	Soluble.	Soluble.
Cobalt.	Blue precipitate; soluble in excess to brown solution.	Insoluble.	Blue; insoluble in excess; turned brownish on heating.	Blue; insoluble in excess; turned brownish on heating.	Blue; insoluble in excess; turned brownish on heating.
Nickel.	Soluble in excess to violet-blue solution.	Insoluble.	Apple-green; insoluble in excess.	Apple-green; insoluble in excess.	Apple-green; insoluble in excess.
Zinc.	Very soluble.	Soluble.	Soluble in large excess; reppted on heating.	Soluble in large excess; reppted on heating.	Soluble in very large excess; reppted on heating.
Cadmium.	Soluble.	Insoluble.	Insoluble.	Insoluble.	Insoluble.
Silver.	Brownish; very soluble in excess.	...	Brownish; soluble in large excess; reppted on warming.	Brownish; soluble in large excess; reppted on warming.	Dirty brown ppte changing to black; sol. large excess to dark solution; reppted on warming.
Cupric.	Blue; soluble in excess to deep blue *solution.*	Soluble with difficulty in excess.	Blue; soluble in large excess to deep blue *solution*; reppted dirty brown on boiling.	Blue; partly soluble in large excess; re-*ppted dirty* brown on boiling.	Blue; partly soluble in large excess; re-*ppted dirty* brown on boiling.
Mercuric.	White.	...	White; insoluble.	White; soluble in much water.	Yellow; changing to very pale yellow.
Stannic.	Insoluble.	Very soluble in excess.	...	Soluble.	Soluble.
Antimonic.	...	...	...	Soluble.	Soluble in large excess.
Gold.	Insoluble.	Soluble.	Brownish *yellow ppt*; readily soluble in excess to orange-red liquid.	Yellow pre-*cipitate*; soluble in excess to brown liquid.	...
Ruthenium.	Insoluble.	Soluble.	...	...	...
Lead.	Insoluble.	...	Insoluble.	Insoluble.	Insoluble.

(*e.g.*, morphine, codeine). It is also produced when caffeine is boiled with baryta-water, and by heating hydrochloride of trimethylamine to 285°, when methyl chloride and trimethylamine volatilise, and methylamine hydrochloride (mixed with some ammonium chloride) remains.

Methylamine may be prepared by the action of alcoholic ammonia on methyl iodide, but in this case dimethylamine and trimethylamine are also produced (page 3), and the main product is iodide of tetramethyl-ammonium. Methylamine is best obtained pure by treating one equivalent of acetamide with two equivalents of bromine, and then adding a 10 per cent. solution of caustic potash till the colour of the bromine has nearly disappeared :—

$$C_2H_3O.NH_2 + Br_2 + 2KHO = C_2H_3O.N.BrK + KBr + 2H_2O.$$

Three additional equivalents of caustic potash are now dissolved to a 10 per cent. solution, and heated in a retort to 70° C. The product of the first reaction is then gradually added through the tubulure. The gases evolved are collected in hydrochloric acid, and on evaporating the solution a mixture of the hydrochlorides of ammonia and methylamine is obtained,[1] from which the latter only is dissolved by absolute alcohol. On distillation with caustic alkali or slaked lime the salt yields the base, quite free from di- or tri-methylamine.

Methylamine boils only a few degrees above zero, and hence is a gas at ordinary temperatures. One volume of water at 12°·5 C. dissolves 1150 measures of the gas, and hence it is more soluble even than ammonia, which methylamine closely resembles in odour and general characters, but is distinguished by its ready inflammability—a property even possessed by its concentrated aqueous solution. It burns with a yellow flame, forming carbon dioxide, water, nitrogen, and hydrocyanic acid.

On passing a succession of electric sparks through methylamine, hydrocyanide of methylamine is produced, and this is decomposed by a continuation of the treatment, with formation of a tarry deposit. When passed through a red-hot tube, methylamine is decomposed with formation of hydrogen and ammonium cyanides, methane, and hydrogen.

The behaviour of methylamine with metallic solutions (page 10) and various other of its reactions have already been described. It forms a series of readily crystallisable salts. The *chloro-*

[1] The reaction which occurs is very complex (A. W. Hofmann, *Ber.*, xv. 765), but the main decomposition may be expressed as follows:—

$$CH_3.CO.NKBr + 2HOK = CO(OK)_2 + KBr + CH_3.NH_2.$$

platinate, $(MeH_3N)_2PtCl_6$, is insoluble in alcohol, but soluble in boiling water, crystallising on cooling in beautiful golden-yellow scales.

A method for the proximate analysis of the bases present in crude methylamine, based on the principles of the process described on page 6, has been described by A. Müller (*Bull. Soc. Chim.*, xlii. 202; *Journ. Chem. Soc.*, xlviii. 501).

Dimethylamine.

$$C_2H_7N = \left.\begin{matrix} CH_3 \\ CH_3 \\ H \end{matrix}\right\} N.$$

Dimethylamine occurs in Peruvian guano and pyroligneous acid, and is also present in the products of the distillation of *vinasses*.

Dimethylamine is readily separated from the primary and tertiary methylamines by converting it into ethyl dimethyloxamate (pages 5, 6, 14), or into dimethylnitrosamine (page 7). On distilling the first of these derivatives with caustic alkali, or treating the second with fuming hydrochloric acid, the dimethylamine is regenerated. The base may also be obtained pure by boiling 35 parts of nitroso-dimethylaniline hydrochloride with a solution of 15 parts of caustic potash in 400 of water:—

$$C_6H_4(NO).NMe_2,HCl + KHO = KCl + C_6H_4(NO).OH + HNMe_2.$$

Dimethylamine boils at 8°–9° C., and closely resembles the primary and tertiary methylamines. From the former it is at once distinguished by the non-formation of a precipitate on the addition of ethyl oxalate to the aqueous solution of the base (page 6), and the non-production of an isonitrile on treatment with alcoholic potash and chloroform. From trimethylamine it is distinguished by the formation of a nitrosamine on treating it with nitrous acid, or one of its salts with a nitrite (page 7).

The *chloroplatinate*, $(Me_2H_2N)_2PtCl_6$, crystallises in very long needles.

Trimethylamine.

$$C_3H_9N = \left.\begin{matrix} CH_3 \\ CH_3 \\ CH_3 \end{matrix}\right\} N.$$

Trimethylamine, often improperly called propylamine, a base having the constitution $(C_3H_7)H_2N$, occurs somewhat frequently both in the animal and vegetable kingdom. In the former it occurs notably in herring-brine, and has been detected in urine, unputre-

fied blood of the calf, cod-liver oil, and other animal fluids. In the vegetable kingdom, trimethylamine occurs in the *Chenopodium vulvaria* (stinking goose-foot), from the leaves of which it constantly exudes; *Arnica montana; Mercurialis annua;* the blossoms of the pear, white-thorn (*Cratægus oxyacantha*), hawthorn, and wild cherry; and in ergot[1] and other parasites of the vegetable kingdom. Trimethylamine is also a product of the dry distillation of certain alkaloids, wood, &c., but especially of the *vinasses* or residue left after the distillation of the spirit from fermented beetroot molasses. The bases obtained by the destructive distillation of this product are derived from the b e t a i n e, $C_5H_{10}NO_2$, contained in the molasses, and consist chiefly of the monamines of methyl, among which trimethylamine predominates.[2]

The products of the destructive distillation of the "vinasses," left after the distillation of the fermented beetroot-molasses, vary with the concentration of the liquid. As the proportion of water decreases, the quantity of ammonia increases, and the trimethylamine is replaced by the primary and secondary methylamines. The *vinasses* from different localities yield varying proportions of gaseous and liquid products on distillation, the nitriles and methylic alcohol appearing to be the most variable constituents.[3]

[1] The trimethylamine of ergot is probably a decomposition-product of c h o l i n e, $(CH_3)_3N(C_2H_4OH).OH$.

[2] The *vinasses*, or spent wash from the stills, is evaporated till it acquires a specific gravity of 1·31, when it is subjected to dry distillation in cast-iron retorts. The aqueous portion of the distillate contains :—Ammonium carbonate, sulphydrate and cyanide; methyl alcohol, methyl sulphide, and methyl cyanide; various other bodies of the fatty series; and a large proportion of salts of trimethylamine. The tar yields, on distillation :—ammoniacal liquor, various oils, pyridine bases, solid hydrocarbons, phenols, and pitch of superior quality. The aqueous liquid is neutralised with sulphuric acid and concentrated, when crystals of ammonium sulphate are deposited, and vapours of methyl alcohol are evolved together with methyl cyanide and other nitriles. The methyl cyanide is converted in ammonia and acetate by treatment with an alkali :—$CH_3.NC + NaHO + H_2O = H_3N + CH_3.COONa$. The dark-coloured mother-liquors retain the trimethylamine sulphate, which is decomposed by distillation with lime, the vapours being passed into hydrochloric acid. The resultant solution is boiled down till the temperature reaches 140° C. Ammonium chloride crystallises out on cooling, and the mother-liquor is separated and concentrated till the boiling-point rises to 200°, the product forming c o m m e r c i a l h y d r o c h l o r i d e o f t r i m e t h y l a m i n e, from which the free base may readily be obtained by treatment with lime or caustic alkali.

[3] In a specimen of "commercial trimethylamine," prepared from vinasses, D u v i l l i e r and B u i s i n e found only from 5 to 10 per cent. of trimethylamine and some 50 per cent. of dimethylamine; while the remainder consisted of methylamine, propylamine, and isobutylamine in about equal proportions;

Trimethylamine has a specific gravity of 0·673 at 0°, and boils between 9° and 10° C. When pure and concentrated, trimethyl-

the ethylamine being estimated at about 2 per cent., and ammonia being absent (*Compt. Rend.*, lxxxix. 48). The method employed by these chemists for the separation of the amines in question was as follows (*Ann. Chim. Phys.*, [5], xxiii. 289):—The aqueous solution of the free bases was treated with ethyl oxalate, the dense white precipitate of oxamides filtered off, the filtrate concentrated by distillation, and the further precipitate added to that previously obtained. By treating the precipitate with hot water it was separated into three fractions. The most insoluble portion (1) consisted of dibutyloxamide (or possibly di-*iso*butyloxamide), which melted and floated on the hot water, and on cooling formed a solid waxy mass. When recrystallised from alcohol, it was obtained in pearly needles. The *butylamine*, $C_4H_9NH_2$, obtained by distilling the oxamide with potash, had a faintly aromatic odour, and yielded a slightly soluble chloroplatinate, crystallising in orange-coloured plates. Of the oxamides soluble in boiling water, the dipropyl compound (2) was first deposited. It crystallised from alcohol in pearly needles melting at 110°, and the *propylamine*, $C_3H_7.NH_2$, obtained from it gave an orange chloroplatinate. When the proportion of butylamine and propylamine was small, the authors preferred to utilise the comparative insolubility of their sulphates in alcohol to separate them from the other amines. The most soluble portion of the mixed oxamides (3) was deposited in opaque white needles or grains, and consisted of dimethyloxamide. The base obtained by distilling it with potash was converted into the sulphate, which on treatment with boiling absolute alcohol was obtained quite pure, and yielded pure *methylamine* on treatment with potash.

The mother-liquor separated from the oxamides of the primary amines was distilled with caustic potash, and the dried gas collected in absolute alcohol. A portion of the solution was then titrated with standard acid, and the remainder gradually added to a quantity of ethyl oxalate sufficient for the reaction:—$Me_2NH + Et_2C_2O_4 = (MeHN)_2C_2O_2 + 2EtOH$; assuming the alkalinity to be wholly due to dimethylamine. The operation was conducted in a flask, which was surrounded with ice and continually shaken. When the reaction was completed, the flask was heated on the water-bath, and the alcohol and unchanged *trimethylamine* distilled off and collected in hydrochloric acid. It yielded a chloroplatinate in large orange-red crystals, and was the only tertiary amine found in the mixture of bases under examination.

The syrupy residue left in the flask after the distillation of the alcohol and trimethylamine consisted of the ethyl dialkylated-oxamates, with traces of ethyl monalkylated-oxamates and oxamides of primary amines. It was treated with water, which caused hydrolysis; and, on neutralising the liquid with milk of lime, calcium ethyloxamate and propyloxamate were thrown down, which on distillation with potash yielded *ethylamine*, $C_2H_5.NH_2$, and *propylamine*, $C_3H_7.NH_2$. On treating the filtrate from the calcium oxamates precipitate with an equal volume of alcohol, a precipitate was formed from which warm water extracted calcium dimethyloxamate, yielding *dimethylamine*, $(CH_3)_2NH$, on distillation with potash, while the less soluble portion consisted of calcium monomethyloxamate, yielding *methylamine* under similar treatment.

Ethylamine, which escaped detection on Duvillier and Buisine's first

amine is stated to have a purely ammoniacal odour; but when highly diluted, the vapour has at the same time a smell of ammonia and a peculiar fishy odour suggestive of herring-brine. The latter odour is gradually developed by adding lime to a solution of the base, but requires some time to reach its maximum intensity (L. Taylor).

Trimethylamine is apparently soluble in all proportions of cold water.[1]

A mixture of equal measures of trimethylamine and water is inflammable.

Trimethylamine is employed for preparing pure potassium carbonate from the chloride by a method analogous to the ammonia-soda process. Ammonia is not available, because of the nearly equal solubility in water of ammonium chloride and acid potassium carbonate, whereas the hydrochloride of trimethylamine is much more soluble.

Trimethylamine might, *primâ facie*, be supposed the active agent in Wollheim's process of treating sewage with herring-brine and lime (*Eng. Patent* No. 15321, 1888); but those who have investigated the matter incline to the opinion that the bactericide is a hitherto unisolated body they term aminol, produced by the action of lime on one of the amines of herring-brine. Pure trimethylamine employed without lime has not the same effect.

Trimethylamine is distinguished from the primary and secondary methylamines by its negative reaction with alcoholic potash and chloroform (page 7), ethyl oxalate (page 5), and nitrous acid (page 7), and by its solution in excess of hydrochloric acid being precipitated by potassium ferrocyanide (page 8).

Trimethylamine has been employed in medicine, and is said to have proved of value in the treatment of gout and acute rheumatism.

examination of the bases from vinasses, owing to the small proportion present, was subsequently detected by distilling with potash the mother-liquors obtained by treating the oxamides with water, and converting the bases into sulphates. On treating these with absolute alcohol, the sulphate of methylamine remained. On distilling the soluble portion with alkali, collecting the bases in absolute alcohol, and treating the solution with ethyl oxalate, as already described, the ethylamine was converted into a monoethyloxamate, from which the calcium salt was prepared and decomposed by alkali.

[1] According to Guthrie, the solubility of trimethylamine in water is notably diminished by heating, the liquid becoming distinctly turbid (compare nicotine) from partial separation of the base. Thus a 10 per cent. solution of trimethylamine in water became turbid at 22° C.; an 8 per cent. at 24°·5; and a 4 per cent. solution at about 42° C. Leo Taylor has failed to confirm Guthrie's observations, which were not improbably made on impure material.

(A valuable description of its therapeutic effects will be found in the *Year-Book of Pharmacy* for 1873, pages 197–262.)[1]

Trimethylamine combines with carbon disulphide at the ordinary temperature with great evolution of heat, according to the equation $CS_2 + (CH_3)_3N = N(CH_3)_2.CS.S.CH_3$. The product, which may be regarded as trimethyl-thiocarbamic acid, is prepared more readily by passing gaseous trimethylamine into a mixture of carbon disulphide and alcohol. It is obtained on evaporating the solvent in white rhombic needles, melts at 125°, and decomposes gradually at the ordinary temperature. It is soluble in dilute alcohol and water, but nearly insoluble in absolute alcohol, ether, chloroform, or benzene. Dilute acid combine with it to form salts, but strong acids and alkalies decompose it into carbon disulphide and trimethylamine.

Trimethylamine Hydrochloride. Hydrochlorate of trimethylamine. Chloride of Trimethylammonium. $(CH_3)_3HNCl$. This salt is obtained by neutralising trimethylamine with hydrochloric acid. It differs from ammonium chloride in being extremely deliquescent, and soluble in absolute alcohol. The fishy odour of the base liberated on treating the salt with lime or caustic alkali further distinguishes it from ammonium chloride. With platinic chloride it unites to form the *chloroplatinate*, $(Me_3HN)_2PtCl_6$, a compound which crystallises in orange octohedra, sparingly soluble in absolute alcohol.

When heated to 260°–285° C., trimethylamine hydrochloride is decomposed with formation of free trimethylamine, ammonia, and methyl chloride:—

$$3MeHNCl = 2Me_3N + H_3N + 3MeCl.$$

This reaction has been utilised by Camille Vincent for the manufacture of methyl chloride. The vapours are passed through hydrochloric acid, which absorbs the bases, while the gaseous methyl chloride passes on. It is washed by dilute caustic soda and dried by strong sulphuric acid, after which it is collected in a gas-holder, from whence it is pumped into strong wrought-iron cylinders, in which it is condensed to liquid. The vapour of liquid methyl chloride has a tension of 2·5 atmospheres at 0° and 4·8 at 20° C.

[1] The solution of trimethylamine for medicinal use should be clear, colourless, and of 1·124 specific gravity. It should have a peculiar odour, recalling that of ammonia and herring-brine, be miscible in all proportions with water and alcohol, and contain 20 per cent. of the base. One measure of hydrochloric acid, of 1·170 specific gravity, should neutralise three measures of the solution of the base, and the salt obtained on evaporating the resultant solution should be completely soluble in absolute alcohol.

Methyl chloride is extensively used in the aniline-dye manufacture for preparing methylaniline and dimethylaniline, which compounds form the starting-points of numerous colouring matters.

Ethylamines.

The amines of ethyl are obtainable in the manner already described (page 3). A convenient source of the primary amine, $C_2H_5.NH_2$, is the crude ethyl chloride obtained as a bye-product in the manufacture of chloral (A. W. Hofmann, *Ber.*, iii. 109, 776). When ethyl chloride is heated to 90° under pressure with an equivalent proportion of strong aqueous ammonia, a layer of triethylamine containing ammonia is formed, while the aqueous liquid contains the hydrochlorides of ethylamine and diethylamine. When a similar mixture of aqueous ammonia and ethyl chloride is heated under pressure to 150° C., H_4NCl, EtH_3NCl, and Et_4NCl are the chief products, only traces of Et_2H_2NCl and Et_3HNCl being formed.

The amines of ethyl can be separated by methods already described. They present the closest analogy to the corresponding methyl bases. Various differences between the three amines are described on page 4 *et seq.* The following table shows other of their characteristic properties.

	ETHYLAMINE.	DIETHYLAMINE.	TRIETHYLAMINE.
Formula.	$(C_2H_5)H_2N$	$(C_2H_5)_2HN$	$(C_2H_5)_3N$
Boiling-point, 0° C.	19	56	90
Specific gravity.	$\frac{8}{x}0{\cdot}6964$ $\frac{2}{x}0{\cdot}708$	$\frac{0}{x}0{\cdot}7062$ $\frac{20}{x}0{\cdot}706$	$\frac{20}{x}0{\cdot}7277$
Reaction with zinc sulphate.	Precipitate soluble in excess.	Precipitate insoluble in excess.	Precipitate insoluble in excess.
Product when boiled with nitrous acid (or a salt of the bases with sodium nitrite solution).	Alcohol and nitrogen.	Diethylnitrosamine; a neutral oily liquid boiling at 177°, and distilling with steam (page 7).	Unchanged.
Hydrochloride.	Deliquescent laminæ and prisms.	Non-deliquescent plates.	Non-deliquescent laminæ.
Chloroplatinate.	Hexagonal rhombohedra; moderately soluble in water.	Monoclinic; moderately soluble.	Monoclinic; very soluble.
Acid ferrocyanide.	Soluble.	Soluble.	Very sparingly soluble.

AMMONIUM BASES.

By the action of excess of an alkyl iodide on ammonia or an amine, all the hydrogen atoms of ammonia can be replaced by alkyl radicals, the tertiary amines thus formed combining with another molecule of alkyl iodide to produce the iodide of a tetra-alkylated ammonium. When methyl iodide has acted on ammonia, the product is tetramethyl-ammonium iodide, $(CH_3)_4NI$; but by obvious modifications in the process, similar compounds containing other alkyl-radicals can be obtained. Thus, Hofmann prepared the iodide of methyl-ethyl-amyl-phenyl-ammonium:—$(CH_3)(C_2H_5)(C_5H_{11})(C_6H_5)NI$.

The same product results from the action of ethyl iodide on trimethylamine as by the action of methyl iodide on dimethyl-ethylamine. This fact proves that the body formed is not merely a molecular compound of the constitution

$$\left.\begin{matrix} CH_3 \\ CH_3 \\ CH_3 \end{matrix}\right\} N,C_2H_5I \; ; \text{ or } \left.\begin{matrix} CH_3 \\ CH_3 \\ C_2H_5 \end{matrix}\right\} N,CH_3I \; ;$$

but that it is the true iodide of a tetra-alkylated ammonium:—

$$\left.\begin{matrix} CH_3 \\ CH_3 \\ CH_3 \\ C_2H_5 \end{matrix}\right\} NI$$

The identity of these and similar compounds furnishes important evidence of the pentavalent character of nitrogen.

The iodides of the tetra-alkylated ammoniums are quite unacted on by caustic potash even on heating, but react with recently precipitated argentic oxide to form iodide of silver and the hydroxides of the tetra-alkylated ammoniums. These hydroxides are non-volatile, syrupy or solid deliquescent substances, of highly caustic, alkaline character, presenting, as a class, a strong analogy to caustic potash. Many of them have marked poisonous characters.

Such of the natural vegetable alkaloids as have the constitution of tertiary bases unite with alkyl iodides to form compounds which have the characters of iodides of compound ammoniums, from which the corresponding hydroxides can be prepared, as above described, by reaction with oxide of silver. Thus, for example, from morphine, $C_{17}H_{19}NO_3$, may be prepared:—

Ethylmorphium iodide, ... $\left.\begin{matrix} C_{17}H_{19}O_3 \\ C_2H_5 \end{matrix}\right\} N.I$

Ethylmorphium hydroxide, . . $\left.\begin{matrix} C_{17}H_{19}O_3 \\ C_2H_5 \end{matrix}\right\} N.OH$

These bodies are sometimes formulated and described as the hydriodide and hydrate of ethylmorphine, $C_{17}H_{18}(C_2H_5)NO_3$; but such a view is inconsistent with their characters.

Similar bodies are obtained by action of alkyl iodides on strychnine. The hydroxides of methyl- and ethyl-strychnium ($C_{21}H_{22}MeNO_2.OH$ and $C_{21}H_{22}EtNO_2.OH$) are strong, very soluble bases, which form carbonates and precipitate metallic hydroxides from metallic solutions. In their physiological action they simulate the paralysing action of curarine rather than the tetanic poisoning of strychnine itself.

Similar bases can be obtained by the action of alkyl salts on diamines or ammonia. Thus, an end-product of the action of excess of ethylene dibromide on ammonia is tetra-ethylene-di-ammonium-dibromide $(C_2H_4)_4N_2Br_2$, from which the hydroxide, $(C_2H_4)_4N_2.OH$, can be obtained by treatment with oxide of silver. This base is a powerful caustic alkali and non-volatile.

Choline and neurine, described in the chapter on "Animal Bases," are natural products having the constitution of ammonium bases. Thus :—

CHOLINE. Trimethyl-hydroxyethyl-ammonium hydroxide, . . $\left.\begin{matrix}(CH_3)_3\\(C_2H_4.OH)\end{matrix}\right\}N.OH$

NEURINE. Trimethyl-vinyl-ammonium hydroxide, . . $\left.\begin{matrix}(CH_3)_3\\(C_2H_3)\end{matrix}\right\}N.OH$

It will be observed that neurine and choline only differ from each other by the elements of water.

Bases of similar characters and constitution have been prepared, containing phosphorus, arsenic, or antimony in place of nitrogen. Thus, there have been obtained :—

Tetramethyl-ammonium hydroxide, . .	$Me_4N.OH$
Trimethyl-ethyl-phosphonium hydroxide, .	$Me_3EtP.OH$
Tetrethyl-arsonium hydroxide, . .	$Et_4As.OH$
Tetrethyl-stibonium hydroxide, . .	$Et_4Sb.OH$

Tetrethyl-ammonium Compounds.

When perfectly anhydrous ethyl iodide is added to trimethylamine previously dried over caustic potash, combination gradually occurs with evolution of heat, and in a few days the mixture sets to a solid mass of

Tetrethylammonium Iodide, $(C_2H_5)_4NI$. This compound is preferably prepared by exposing a mixture of equivalent proportions of triethylamine and ethyl iodide to a temperature of 100° for a

few minutes in a flask furnished with a well-cooled inverted condenser, or preferably in a sealed tube. Violent reaction ensues, and, on cooling, the product sets to a hard mass of crystals. On dissolving the mass in water, and allowing the solution to evaporate spontaneously, the iodide is obtained in extremely bitter crystals of considerable size, which, when pure, are colourless, but are apt to be mixed with reddish crystals of the tri-iodide, $(C_2H_5)_4NI,I_2$.[1]

Tetrethylammonium iodide is not volatile at 100° C., but when rapidly heated in a retort to a higher temperature it melts and suffers decomposition into ethyl iodide and trimethylamine, which form separate layers in the receiver but re-unite to produce the original compound.

Tetrethylammonium iodide is wholly undecomposed by treatment with caustic potash or soda, but is much less soluble in caustic alkaline solutions than in water. Hence, on adding excess of caustic potash to its concentrated aqueous solution, a solid crystalline mass is produced. This behaviour sharply distinguishes the iodide of tetrethyl-ammonium (and of other compound ammoniums) from the compounds Et_3HNI, Et_2HNI, and EtH_3NI, which are at once decomposed by caustic alkali, with liberation of the corresponding amine. The aqueous solution of tetrethylammonium iodide reacts with argentic nitrate or sulphate to form a precipitate of argentic iodide and a solution of the tetrethylammonium nitrate or sulphate.

Tetrethylammonium Hydroxide, $(C_2H_5)_4N.OH$, is obtained in solution by adding freshly-precipitated oxide of silver to a dilute and warm solution of tetrethylammonium iodide, until the brown colour of the silver oxide ceases to change into the lemon-yellow of the iodide. The solution is then filtered, and may be evaporated to a considerable extent at a gentle heat, but further concentration must be conducted *in vacuo*, at the ordinary temperature, over sulphuric acid and lime. Long, hair-like, deliquescent needles of the base are deposited, but these subsequently disappear, and the liquid ultimately dries up to a semi-solid mass.

Tetrethylammonium hydroxide presents the closest analogy to caustic potash. It is highly deliquescent, absorbs carbon dioxide from the air, and the aqueous solution has a strong alkaline reaction. It has an alkaline, caustic, and extremely bitter taste, and in a concentrated state burns the tongue and acts on the skin like caustic potash. With metallic solutions it behaves like the caustic alkalies, except that aluminium hydroxide is soluble with

[1] This compound is readily obtained by dissolving iodine in a solution of tetrethylammonium iodide.

difficulty in excess of the reagent, and chromic hydroxide is quite insoluble.

A moderately strong solution of tetrethylammonium hydroxide may be boiled without decomposition; but in a concentrated state, even at 100°, the liquid froths strongly, and the base is resolved gradually but completely into triethylamine, ethylene, and water:—$(C_2H_5)N.OH = (C_2H_5)_3N + C_2H_4 + H.OH$.[1] This reaction affords a convenient means of obtaining triethylamine unmixed with the primary and secondary amines.

When a solution of tetrethylammonium hydroxide is boiled with a slight excess of ethyl iodide for twenty-four hours, under a reflux condenser, the solution becomes perfectly neutral, the following reaction occurring:—$(C_2H_5)_4N.OH + C_2H_5I = (C_2H_5)_4NI + C_2H_5.OH$.

Tetrethylammonium hydroxide also hydrolyses ethyl oxalate, and saponifies fats as readily as caustic potash.

On adding caustic potash and potassium iodide to a strong solution of tetrethylammonium hydroxide, a white crystalline mass of tetrethylammonium iodide is produced.

The *salts* of tetrethylammonium are mostly crystallisable and readily soluble.

Tetrethylammonium Chloride, $(C_2H_5)_4NCl$, obtained by neutralising the hydroxide with hydrochloric acid, is crystalline and highly deliquescent. It forms double salts with auric, mercuric, and platinic chlorides. *Tetrethylammonium chloroplatinate*, $(Et_4N)_2PtCl_6$, is thrown down immediately as an orange-yellow precipitate, consisting of microscopic octahedra, on adding platinic chloride to a solution of tetrethylammonium chloride. It is slightly soluble in water, and less soluble in alcohol and ether.

[1] Collie and Schryver (*Jour. Chem. Soc.*, lvii. 767) have recently shown that when a *mixed* quaternary-ammonium chloride or hydroxide (made from trimethylamine or triethylamine) is heated, a mixed tertiary amine is always produced in greater or less amount. With triphenylmethylammonium the only product is dimethylphenylamine, while with the allyl- and isopropyl-trimethylammonium compounds, the chief tertiary amine formed by the action of heat is trimethylamine. In the case of the chlorides, the methyl-group is very easily eliminated as methyl chloride; whilst in the case of the hydroxides, the ethyl-group almost invariably splits away as ethylene. (See a later paper by Schryver on the asymmetry of nitrogen in substituted ammonium compounds. *Proc. Chem. Soc.*, 1891, page 39.)

HYDRAZINES.

THE name hydrazine was first applied by E. Fischer to a hypothetical base, having the constitution of diamidogen, $H_2N.NH_2$. Since then the base itself has been obtained in the form of a hydrate, and possibly also in the free state.

Hydrazine. Diamidogen. Diamide. N_2H_4 or $H_2N.NH_2$.

Hydrazine is obtained by the decomposition of triazo-acetic acid by heating it with water or mineral acids, when the following reaction occurs :—

$$\underset{\text{Triazo-acetic acid.}}{C_3H_3N_6(COOH)_3} + \underset{\text{Water.}}{6H_2O} = \underset{\text{Hydrazine.}}{3N_2H_4} + \underset{\text{Oxalic acid.}}{3C_2H_2O_4}.$$

The oxalic acid is more or less split up, according to the temperature and the strength of the acid employed, into carbonic and formic acids, so that when only water is used the hydrazine separates as a formate; but if a mineral acid be present it forms the corresponding salt.

Hydrazine has an extraordinary affinity for water, readily forming a hydrate, N_2H_4,H_2O, which it does also when set free from its salts by caustic alkalies or lime.[1] This hydrate is a liquid fuming in the air and boiling unaltered at 119° C., and can be easily separated from water by distillation, though some of it passes over with the steam. When heated with barium oxide in a sealed tube to 170°, some anhydrous hydrazine appears to be formed and escapes as a white fume on opening the tube.

The solution of hydrazine turns reddened litmus-paper a deep blue, and gives white fumes with acid vapours. In a concentrated state it has a very peculiar odour, only slightly resembling that of

[1] Hydrazine hydrate is best prepared (Curtius and Schultz) by distilling a mixture of eleven parts of hydrazine sulphate with four of caustic potash and one of water in a silver retort provided with a silver condenser. When the last drop has passed over, the distillate is fractionated. After four fractionations the last portions boil constantly at 119°. Curtius and Jay (*Jour. Pract. Chem.*, [2], xxxix. 27) prepare hydrazine hydrate by heating the hydrochloride of the base with caustic lime in a silver retort, and passing the vapours through a heated silver tube containing caustic lime.

ammonia. It powerfully affects the nose and throat, has an alkaline taste, and leaves a burning sensation on the tongue. When boiling, the solution attacks glass, and quickly destroys corks and india-rubber. Hydrazine, like hydroxylamine, is a strong poison of universal character.

Hydrazine reduces Fehling's solution and ammonio-nitrate of silver in the cold. With cupric sulphate it yields a red precipitate (? cuprous oxide), with mercuric chloride a white precipitate, and precipitates alumina from a solution of alum. With aromatic aldehydes and ketones it yields sparingly soluble crystalline compounds.

SALTS OF HYDRAZINE.

Hydrazine combines with one or two molecules of monobasic acids to form very stable salts, which are usually crystalline and isomorphous with the corresponding ammonium salts. The salts Hz,2HR crystallise in the regular system and are readily soluble in water, but nearly insoluble in alcohol. The mono-acid salts, HzHR, are easily soluble in water and warm alcohol, from which they crystallise well. The salts of both classes are insoluble in ether, benzene, &c. In acid solution, the salts of hydrazine possess remarkably strong reducing properties, and are powerfully toxic towards the lower organisms. Peptone solutions containing 0·1 per cent. of hydrazine sulphate are unable to support bacterial life.

Hydrazine Dihydrochloride, $N_2H_4,2HCl$, crystallises from hot water in large glassy octahedra that are freely soluble in water, but less so in alcohol. On treatment with platinic chloride it does not yield a chloroplatinate, but is decomposed with evolution of much nitrogen. It melts at 198° C., with evolution of hydrochloric acid, to a clear glass consisting of the *monohydrochloride*, N_2H_4,HCl, and this on further heating to 240° C. is decomposed into ammonium chloride, nitrogen, and hydrogen.

Hydrazine Sulphate, N_2H_4,H_2SO_4, according to T. Curtius, is best obtained from ethyl diazo-acetate, which on treatment with hot concentrated caustic potash yields the potassium salt of an acid which separates in golden yellow tablets on addition of a mineral acid. On digesting the yellow aqueous solution of these with very dilute sulphuric acid, the colour disappears without evolution of gas, and on cooling crystals of the sparingly soluble hydrazine sulphate are obtained. From the sulphate, other salts of hydrazine may be prepared by double decomposition with barium salts.

Salts of hydrazine in solution are decomposed by sodium nitrite, with evolution of gas attended by much frothing. The reaction is analogous to the decomposition of ammonia salts by a nitrite, with the difference that whereas in the latter case (*a*) nitrogen is

tinguished from the latter by their capacity of reducing Fehling's copper solution, in many instances at the ordinary temperature. The product of the oxidation of the hydrazine is the corresponding amine. Thus, diethyl-hydrazine, $(C_2H_5)_2N.NH_2$, is oxidised to diethyl-amine, $(C_2H_5)_2HN$.

The general and special characters of the hydrazines are sufficiently exemplified by two typical species, ethyl-hydrazine and phenyl-hydrazine.

Ethyl-hydrazine. $C_2H_8N_2 = (C_2H_5)HN.NH_2$.

On treating diethyl-urea with nitrous acid, a nitroso-compound is formed, which on reduction with zinc-dust and acetic acid is converted into a body called diethyl-semicarbazide.

$$CO\begin{cases} NH(C_2H_5) \\ NH(C_2H_5) \end{cases} \qquad CO\begin{cases} NH(C_2H_5) \\ N(NO)(C_2H_5) \end{cases} \qquad CO\begin{cases} NH(C_2H_5) \\ N(NH_2)(C_2H_5) \end{cases}$$

Diethyl-urea. Nitroso-compound. Diethyl-semicarbazide.

This last body decomposes, on heating with strong hydrochloric acid, into ethyl-hydrazine, ethylamine, and carbon dioxide:—

$$NH(C_2H_5).CO.N(NH_2)C_2H_5 + H_2O = HN.(NH_2)(C_2H_5) + HNH(C_2H_5) + CO_2.$$

The ethylhydrazine hydrochloride is less soluble than the corresponding salt of ethylamine, and may be separated from it by crystallisation.

Ethylhydrazine is a colourless, mobile liquid of ethereal and faintly ammoniacal odour. It boils at 100°, and distils undecomposed. It is very hygroscopic, forming white fumes with moist air, dissolves in water and alcohol with evolution of heat, and corrodes cork and caoutchouc.

Ethylhydrazine gives Hofmann's isonitrile reaction for primary amines with chloroform and alcoholic potash (page 7). Bromine decomposes it with evolution of nitrogen, and it is also decomposed by nitrogen trioxide.

Ethylhydrazine is a very powerful deoxidising agent. It reduces Fehling's copper solution at the ordinary temperature, reduces argentic oxide, and converts oxide of mercury into mercuric ethide, $Hg(C_2H_5)_2$. It yields a black precipitate with Nessler's solution.

Ethylhydrazine reacts with aldehydes, with evolution of heat, to form ethyl-hydrazides, $R.CH:N_2H(C_2H_5)$.

Potassium anhydrosulphite, $K_2S_2O_7$, reacts on ethylhydrazine to form potassium ethyl-hydrazine sulphite,

$$(C_2H_5)HN.NH(SO_3K),$$

which, on treatment with mercuric oxide, gives potassium diazo-ethane-sulphonate, $C_2H_5.N{:}N.(SO_3K)$, a substance which explodes violently when warmed, and otherwise resembles the diazo-benzene-sulphonates (Part I. page 137).

DIETHYL-HYDRAZINE, $(C_2H_5)_2N.NH_2$, is obtained by the reduction of the nitroso-derivative of diethylamine:—$(C_2H_5)_2N.NO + 2H_2 = (C_2H_5)_2N.NH_2 + H_2O$. It boils at 98°, and closely resembles ethylhydrazine, but does not reduce Fehling's solution unless the liquid is heated. It unites with ethyl iodide to form the body $(C_2H_5)_3N_2H_2I$, which on treatment with oxide of silver yields a strongly alkaline solution of triethylazonium hydroxide, $(C_2H_5)_3N_2H_2.OH$, a powerful base analogous to tetrethylammonium hydroxide (page 20), and which, when heated with water, decomposes into ethylene, diethyl-hydrazine, and water. Mercuric oxide, even in the cold, converts diethyl-hydrazine into tetraethyl-tetrazone, $(C_2H_5)_2N.N{:}N.N(C_2H_5)_2$, a colourless, strongly basic oil, volatile with steam and yielding a metallic mirror with ammonio-nitrate of silver.

Phenyl-hydrazine. $C_6H_8N_2 = (C_6H_5)HN.NH_2$.

Phenylhydrazine is prepared by the action of reducing agents on diazobenzene compounds, $C_6H_5N{:}NX$ (Part I. page 176). Thus diazobenzene chloride may be reduced by the calculated amount of stannous chloride and hydrochloric acid; or the potassio-sulphite with zinc-dust and acetic acid, the product being subsequently decomposed by boiling with hydrochloric acid:—

$$C_6H_5.HN.NH.SO_3K + HCl + H_2O = KHSO_4 + C_6H_5.HN.NH_2,HCl.$$ [1]

Phenylhydrazine is a yellow oil of a faint aromatic odour. It solidifies at low temperatures to a crystalline mass, melts at 23°, and boils, with slight change and evolution of ammonia, at 241°–242°.

[1] Phenylhydrazine is best obtained, as described by V. Meyer, by dissolving 1000 parts of aniline in 2000 parts of strong hydrochloric acid, cooling the solution by means of ice, and then slowly adding an ice-cold solution of 75 parts of sodium nitrite in 400 c.c. of water. To the cold solution of diazo-benzene chloride, $C_6H_5.N{:}N.Cl$, so obtained, a solution of 450 parts of stannous chloride in an equal weight of hydrochloric acid is then added. The mixture soon sets to a white crystalline pulp of phenylhydrazine hydrochloride, $C_6H_5NH_2,HCl$, which is filtered or strained off, and washed with a mixture of alcohol and ether. The free base is obtained by dissolving the hydrochloride in water, adding caustic soda, and agitating with ether, which is separated and evaporated. The product may be purified by distillation.

It volatilises in a current of steam, but not very readily. Phenylhydrazine dissolves sparingly in cold water, more readily in hot, and very readily in alcohol, ether, chloroform, and benzene.

Phenylhydrazine is readily oxidisable, and becomes red and ultimately dark brown on exposure to air, from absorption of oxygen.

Phenylhydrazine has well-marked antiseptic properties, and a 0·1 per cent. solution of the hydrochloride has been recommended as a substitute for one of mercuric chloride of equal strength (*Pharm. Jour.*, [3], xix. 608).

Under certain undetermined conditions, contact of phenylhydrazine with the skin produces troublesome sores.

Phenylhydrazine has well-marked basic properties, and forms well-crystallised salts. The *hydrochloride*, prepared as already described, crystallises from hot water in small, thin, lustrous plates, and is almost completely precipitated from its aqueous solution by concentrated hydrochloric acid, a reaction by which phenylhydrazine may be readily separated from aniline and several other bases.

Solutions of the hydrochloride and other salts of phenylhydrazine act as powerful reducing agents. They reduce the salts of silver, mercury, gold, and platinum in the cold. Freshly-precipitated mercuric oxide is reduced, a salt of diazobenzene being reproduced. Fehling's solution is reduced in the cold, with evolution of nitrogen and precipitation of cuprous oxide, aniline and benzene being simultaneously formed.

If phenylhydrazine hydrochloride be treated with a cold solution of potassium nitrite, a nitroso-compound, $C_6H_5(NO)N.NH_2$, separates in yellow flocks, which, on treatment with phenol and strong sulphuric acid, yield a brown solution, changing to green and blue. This reaction, observed by Liebermann, is common to all nitroso-derivatives.

Phenylhydrazine combines directly with carbon dioxide, carbon disulphide, and cyanogen. The sulphonic acid (para) is employed for the preparation of *tartrazin* (Part II. page 288) and other dyes.

PHENYLHYDRAZIDES. The acetyl-derivative of phenylhydrazine, $C_6H_5.HN.NH(C_2H_3O)$, which may be regarded as acet-phenylhydrazide, has powerful antipyretic properties, and has been introduced into German pharmacy under the name of "hydracetin." The same substance is said to be the active ingredient of the preparation known as "pyrodine" (*Pharm. Journ.*, [3], xix. 425, 508, 1049). Both substances seem to be uncertain in their action and dangerous in use; in fact, hydracetin is reported by Renvers to be a direct blood-poison, the antithermic properties of which are really due to destruction of the red corpuscles.

"Orthine" is the name given by R. Kobert to a body having the constitution of an orthohydrazine-parahydroxybenzoic acid:—

$$C_6H_3 \begin{cases} (OH)^{(1)} \\ (HN.NH_2)^{(2)} \\ (CO.OH)^{(4)}. \end{cases}$$

The free base is very unstable; but the hydrochloride is stable, reduces the persalts of the heavy metals, and possesses a marked antiseptic action.

Phenylhydrazine in aqueous solution reacts very readily with the hydroxy-acids of the sugar group (*e.g.*, gluconic and galactonic acids, $C_5H_6(OH)_5.COOH$; arabinose-carboxylic acid, $C_6H_{12}O_7$) with elimination of water, to form crystalline phenylhydrazides, $R.CO.HN.NH(C_6H_5)$. They are prepared by treating a 10 per cent. solution of the acid or its lactone with a moderate excess of phenylhydrazine and an equal quantity of 50 per cent. acetic acid, and heating the mixture to 100° for 80 to 120 minutes. The hydrazide sometimes crystallises from the hot solution, but more usually separates on cooling. Any free mineral acid should be neutralised by soda before adding the hydrazine, and bromides, chlorides, and sulphates should be got rid of by adding acetate of lead. If sugar be present, the osazone formed can usually be separated from the hydrazide by crystallisation from hot water. The products are beautifully crystalline, those derived from monobasic acids being but little soluble in cold, and only with difficulty soluble in hot water, while those from polybasic acids (*e.g.*, saccharic, metasaccharic, and mucic) are still less readily soluble. The compounds from isomeric acids usually present a close resemblance in their physical properties, but the acids from which they are derived can be regenerated (in a pure state) by boiling the hydrazide for half an hour with thirty volumes of 10 per cent. baryta water, which treatment hydrolyses them completely. From the product, the phenylhydrazine is extracted by agitation with ether, and the aqueous liquid, with any precipitate which may have been formed, is boiled and treated with sulphuric acid in quantity sufficient to precipitate the barium as $BaSO_4$. The filtered liquid yields the free acid or lactone on evaporation (Fischer and Passmore, *Ber.*, xxii. 2728; *Jour. Chem. Soc.*, lviii. 152).

The hydrazides are colourless and readily hydrolysed by alkalies and baryta. They can be readily distinguished from the hydrazones by the reddish violet coloration they give when dissolved in strong sulphuric acid and treated with a drop of ferric chloride solution.

HYDRAZONES. Phenylhydrazine behaves in a highly interesting manner with bodies having the constitution of aldehydes and ketones, with which it reacts with elimination of water to form compounds called hydrazones. Most of the bodies of this class are solid and crystalline, and therefore well suited for the recognition of the aldehydes or ketones producing them. The reaction appears to be general for bodies containing the carbonyl group, CO. The reaction is sometimes complicated by the presence of other reactive groups. Thus compounds containing the α-ketone-alcohol group,—CH(OH).CO—, react in the cold with only one molecule of phenylhydrazine to form colourless compounds containing the group:—$CH(OH).C.(N.NHC_2H_5)$—.

OSAZONES. When the compound thus formed is heated with excess of phenylhydrazine, the alcohol group undergoes dehydrogenisation, reacting at the same time with a second molecule of phenylhydrazine and giving rise to a yellow compound containing the complex group,—$C(N.NHC_6H_5).C(N.NHC_6H_5)$—. Compounds of this kind, in which two hydrazine-residues are attached to two contiguous carbon-atoms, are called osazones, and may be obtained directly by the action of phenylhydrazine on the di-ketones. They are of interest in connection with the carbohydrates, which may frequently be recognised by means of their characteristic osazones (E. Fischer, *Ber.*, xvii. 579; xx. 821). Von Jaksch (*Jour. Chem. Soc.*, l. 744) recommends a solution of phenylhydrazine hydrochloride containing sodium acetate for the detection of sugar in urine.

PYRAZOLINES. An unsaturated hydrocarbon group (*e.g.*, allyl, C_3H_5), if contiguous to the carbonyl group, may also react with phenylhydrazine:—

$$\underset{\text{Acrolein.}}{CH_2{:}CH.COH} + \underset{\text{Phenylhydrazine.}}{C_6H_5.HN.NH_2} = \underset{\text{Water.}}{H_2O} + \underset{\text{Phenyl-pyrazoline.}}{\begin{array}{l} N\text{———}N.C_6H_5 \\ \| \qquad\qquad | \\ CH.CH_2.CH_2 \end{array}}$$

Pyrazolones.

The pyrazolones are derivatives of a body of the formula $C_3H_4N_2O$, the synthesis of which has been effected by Balbiano (*Ber.*, xxiii. 1103). The relationship of pyrazolone to pyrazol, pyrazoline, and pyrazine is shown by the following formulæ:—

$$\underset{\textit{Pyrazol.}}{HN\begin{Bmatrix} N{:}CH \\ CH{:}CH \end{Bmatrix}} \quad \underset{\textit{Pyrazoline.}}{HN\begin{Bmatrix} N{:}CH \\ CH_2.CH_2 \end{Bmatrix}} \quad \underset{\textit{Pyrazolone.}}{HN\begin{Bmatrix} N{:}CH \\ CO.CH_2 \end{Bmatrix}} \quad \underset{\textit{Pyrazine.}[1]}{HN\begin{Bmatrix} NH_2.CH_2 \\ CH_2.CH_2 \end{Bmatrix}}$$

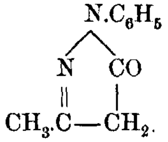
[1] This body must not be confounded with piazine, which was formerly called pyrazine, and probably has the constitution:—

$$N\begin{matrix} \diagup CH{:}CH \diagdown \\ \longrightarrow \\ \diagdown CH{:}CH \diagup \end{matrix}N$$

(See A. T. Mason, *Jour. Chem. Soc.*, lv. 97.)

PHENYL-PYRAZOLONE, $C_6H_5.C_3H_3N_2O$, is obtained by heating phenylhydrazine and iodopropionic acid together to 100°, and treating the product, in chloroform solution, with mercuric oxide.

PHENYL-METHYLPYRAZOLONE, $C_{10}H_{10}N_2O$;



; or $C_6H_5.N\left\{\begin{matrix} N:C(CH_3) \\ CO.CH_2 \end{matrix}\right\}$

When phenylhydrazine is added to ethylic aceto-acetate, $CH_3.CO.CH_2.CO.O(C_2H_5)$, the two bodies react in the cold, with elimination of water, to form $CH_3.C(N.NHPh)CH_2.CO.O(C_2H_5)$.[1] On heating, the hydrazone thus formed splits up into alcohol and phenyl-methylpyrazolone, a body which was originally regarded by its discoverer, Knorr, as a methyl-oxyquinizine.

To prepare phenyl-methylpyrazolone, 100 parts of phenyl-hydrazine are added to 125 of ethyl aceto-acetate, the water which forms is separated, and the oily product is heated for two hours on a water-bath, until a portion is found to solidify on cooling, or on the addition of ether. The warm mass is poured into and stirred with ether, which removes colouring matter, and the white crystalline product washed with ether, and dried at 100°. The yield is quantitative and the product pure. It is almost insoluble in cold water, ether, and petroleum spirit, more readily in hot water, and easily in alcohol. It crystallises from hot water or alcohol in hard brilliant prisms.[2] The *hydrochloride*, $C_{10}H_{10}N_2O,HCl + H_2O$, melts

[1] ANTITHERMIN. When an aqueous solution of levulinic acid (aceto-propionic acid), $CH_3.CO.CH_2.CH_2.COOH$, is added to an equivalent amount of phenylhydrazine, dissolved in dilute acetic acid, a yellow precipitate is produced of the hydrazone, $CH_3C(N.NHPh).CH_2.CH_2.COOH$. When recrystallised from alcohol, this body forms large colourless, odourless crystals of a slight bitter taste, melting at 98°–99°, and nearly insoluble in water, but soluble in alcohol, ether, and dilute acid. It has met with a limited application as an antipyretic under the name of antithermin. It is decomposed by alkalies with liberation of phenylhydrazine, to which fact it probably owes its physiological activity.

[2] When a mixture of phenylmethyl-pyrazolone and phenylhydrazine is heated to boiling, diphenyl-methylpyrazolone, $C_{20}H_{18}N_4O_2$, is formed. Heated with methyl alcohol or methyl iodide it yields diantipyrine, $C_{22}H_{22}N_4O_2$, melting at 245°, and distinguished from antipyrine by its sparing solubility in water and the melting-point of its picrate (161°). When the body $C_{20}H_{18}N_4O_2$ is treated in alkaline solution with excess of sodium nitrite, and the mixture poured into dilute sulphuric acid, *pyrazol-blue*, $C_{20}H_{16}N_4O_2$, separates in flocks. When crystallised from chloroform it forms blue needles, insoluble in water, dilute acids, and alkalies, and only sparingly soluble in alcohol and ether. Its solutions in chloroform and strong sulphuric

at 96°, and the *chloroplatinate*, $(C_{10}H_{10}N_2O)_2H_2PtCl_6+4H_2O$, in prisms melting at 110°. Phenyl-methylpyrazolone yields crystalline precipitates with salts of many of the heavy metals. With silver nitrate an aqueous solution gives crystals of $C_{10}H_9AgN_2O+C_{10}H_{10}N_2O$. The ultramarine cobalt compound and the orange-yellow uranium salt are especially characteristic.

PHENYL-DIMETHYLPYRAZOLONE. ANTIPYRINE. PHENAZONE.

$C_{11}H_{12}N_2O = C_3N_2H(C_6H_5)(CH_3)_2O$ [Ph : Me : Me = 1 : 2 : 3];[1]

$$\text{or, } CO{:}\left\{\begin{matrix} CH:CMe \\ NPh.NMe \end{matrix}\right\}; \text{ or, } C_6H_5.N{:}\left\{\begin{matrix} N(CH_3).C(CH_3):\\ CO\text{———}CH: \end{matrix}\right\}$$

When phenyl-methylpyrazolone is heated with methyl iodide, a further substitution takes place, with formation of phenyl-dimethylpyrazolone, a substance known generally as "antipyrine," less commonly as "analgesin," and called in the additions to the *British Pharmacopœia* (1890), *phenazone*. It is official in the *German Pharmacopœia* of 1890 under the name of *Antipyrinum*.

Antipyrine is prepared by heating equal parts of phenyl-methylpyrazolone, methyl iodide, and methyl alcohol to 100° in a closed vessel. The dark product is decolorised by boiling with sulphurous acid, the alcohol distilled off, and the residue shaken with strong soda, when the base separates as a heavy oil. This is separated and treated with ether, in which it is sparingly soluble. On separating the ether and evaporating off the solvent, the antipyrine is obtained as a mass of crystals which are purified by recrystallisation from toluene.

Antipyrine forms small, lustrous, rhombic needles or plates, which are odourless, but have a somewhat bitter taste. When perfectly anhydrous it melts at 110° to 112° (*B.P.*, 110°; *G.P.*, 113°), but on exposure to air takes up a small proportion (0·6 per cent.) of water, and in that state melts at 105°–107° C. The hygroscopic water may be driven off by exposing the substance to a temperature of 100°, when the original melting-point is restored.

Antipyrine is soluble in about its own weight of cold water, and in less than half its weight of boiling water. It dissolves in twice

acid has an indigo-blue colour, and gives an absorption-spectrum resembling that of indigo. It is not a substantive dye, is decomposed by strong alkalies, decolorised by chlorine and nitric acid, and converted into disphenyl-methylpyrazolone by reducing agents.

[1] Two isomers of antipyrine have been prepared, and others are capable of existing. The known isomers differ from antipyrine by being less soluble in water, not yielding nitroso-derivatives, and by giving methyl-aniline either when distilled with zinc-dust or heated with hydrochloric acid to 200° under pressure.

its weight of absolute alcohol, but in little more than its own weight of rectified spirit. Antipyrine is soluble in an equal weight of amylic alcohol, and in one and a half times its weight of chloroform, but requires about fifty parts of ether for solution, is difficultly soluble in benzene, and nearly insoluble in petroleum spirit.

On adding strong caustic soda to an aqueous solution of antipyrine, the base separates as a milky precipitate, which speedily collects into oily globules. On adding a little ether, these immediately solidify to white crystals without appreciably dissolving, but they dissolve instantly on adding chloroform (J. C. Waterhouse).

An aqueous solution of antipyrine exhibits no alkaline reaction with litmus or phenol-phthaleïn, but destroys the red colour of an acidulated solution of methyl-orange. Free antipyrine may be determined with accuracy by titration in aqueous or alcoholic solution with methyl-orange.

Antipyrine is a strong monovalent base. Its salts, most of which are soluble, do not readily crystallise, with the exception of the *picrate* (melting at 188°); the *ferrocyanide* $(C_{11}H_{12}N_2O)_2$, H_4Cfy, which forms a crystalline precipitate; the *chloroplatinate*, $(C_{11}H_{12}N_2O)_2,H_2PtCl_6+2H_2O$, which forms yellowish-red prisms melting at about 200°; and the *salicylate* (page 37).

When antipyrine is heated with hydrochloric acid under pressure to 200°, it suffers complete decomposition, yielding much aniline and a small quantity of methylamine, besides other products. On distillation with zinc-dust it yields benzene, aniline, a base boiling at 86°–87°, and other products.

Antipyrine is unchanged by treatment with reducing agents in the wet way, but with oxidising agents it gives a series of interesting reactions (Gay and Fortuné, *Pharm. Jour.*, [3], xviii. 1066). Thus when boiled with potassium chlorate and hydrochloric acid, antipyrine gives a reddish-yellow liquid, which on cooling deposits bright-red oily globules, taken up by chloroform with greenish-yellow colour. A solution of bleaching powder produces no change in the cold, but on heating a brick-red precipitate is formed, and the liquid is coloured yellow. Sodium hypochlorite is said to give the yellow coloration on heating, without any precipitate being formed. Chlorine-water produces no change, and bromine-water a light yellow precipitate, dissolving on heating. Potassium bichromate and permanganate are reduced by acid solutions of antipyrine.

When a solution of iodine in iodide of potassium is added to a solution of antipyrine, a precipitate is formed which disappears on agitation, leaving the solution colourless; but on further addition of

the reagent a permanent brick-red precipitate is produced, perceptible in a dilution of 1 in 20,000. According to Manseau (*Pharm. Jour.*, [3], xx. 162), the point at which a permanent precipitate is formed is perfectly definite, and he suggests that the purity of a sample can be ascertained by titration with a standard solution of iodine. Millard and Stark (*Pharm. Jour.*, [3], xx. 863) find that the point of permanent precipitation depends to a marked degree on the dilution of the antipyrine solution. Thus in a 1 per cent. solution, 1 gramme of antipyrine gives a permanent precipitate after the addition of 3·9 c.c. of decinormal iodine, while with twice the volume of water 7·2 c.c. are required. The authors state that more concordant results are obtainable by using starch as an indicator of the end of the reaction. They dissolve 0·5 gramme of the sample of antipyrine in 200 c.c. of water, add plenty of starch solution, and then drop in decinormal iodine solution gradually until a distinct blue coloration is obtained, which does not disappear on vigorously shaking or stirring the mixture. E. Münzer has described an *iodo-antipyrine*, $C_{11}H_{11}IN_2O$, which forms colourless, tasteless needles, melting at 160°.

An acid solution of mercuric nitrate gives a white precipitate with a solution of antipyrine. 2 c.c. of Millon's reagent and 4 c.c. of a 1 per cent. (neutral) solution of antipyrine give a white precipitate in a yellow liquid; in a solution acid with hydrochloric acid, a yellow precipitate in an orange-yellow liquid, the precipitate eventually becoming red. In a solution ten times more dilute a yellow precipitate and green liquid result, and in an acid solution of 1 part of antipyrine in 20,000, a white precipitate and yellow liquid. 1 c.c. of a saturated solution of mercurous nitrate added to twice its measure of a 1 per cent. solution of antipyrine gives a yellow precipitate floating on a blood-red liquid.

If antipyrine be heated with strong nitric acid till reaction commences, and the liquid be then allowed to cool, a fine purple coloration is produced; on adding water a violet precipitate is thrown down, and the filtered liquid is purple-red.

Nitroso-antipyrine. Several of the foregoing reactions are probably due to the presence of nitrous acid, which (if added in the form of red fuming nitric acid) gives with a 1 per cent. solution of antipyrine a beautiful green coloration, still perceptible when diluted to 1 in 20,000; when the liquid is heated it becomes purple-red. In strong solutions a copious formation of small, green, needle-shaped crystals occurs. These consist of isonitroso-antipyrine, $C_{11}H_{11}(NO)N_2O$, and are best obtained by adding a solution of sodium nitrite to a solution

of antipyrine in acidulated water. The liquid at once becomes bluish green in colour, and an abundant formation of crystals speedily occurs. These may be washed with cold water, and dried at the ordinary temperature.[1] Nitroso-antipyrine explodes when heated to about 200°, is nearly insoluble in water and dilute acids, soluble in alkalies and in acetic acid, moderately soluble in alcohol, and sparingly in chloroform and ether. By treatment with zinc and acetic acid it is converted into an oily base.

The green coloration of antipyrine with nitrous acid is delicate and, to a certain extent, characteristic, but is common to all pyrazolones. A. C. Stark recommends that the test should be applied by dissolving potassium nitrite in a test-tube in a little water, adding excess of strong sulphuric acid, and then filling the tube with the liquid to be tested.

Antipyrine dissolves without colour in pure anhydrous ethyl nitrite, but a green colour is immediately developed on addition of water. When antipyrine is added to spirit of nitrous ether containing free acid, the mixture rapidly acquires a dark-green tint, and green needles of nitroso-antipyrine separate. The reaction (which does not occur if any free acid be neutralised by potassium bicarbonate) derives practical importance from the fact that spirit of nitrous ether and antipyrine are not infrequently dispensed in conjunction. A mixture of the kind is alleged to have been fatal to the patient, but it is very doubtful if the nitroso-derivative of antipyrine was the cause of death; for direct exhibition of the compound to a small rabbit, both hypodermically and by the stomach, in doses commencing at ½ grain, and gradually increased to 4 grains, produced no perceptible toxic effect (*Pharm. Jour.*, [3], xviii. 1085). Similar experiments have been made on dogs (*Pharm. Jour.*, [3], xix. 807).

Antipyrine gives a very delicate and characteristic reaction with ferric chloride, which, in a 1 per cent. solution, produces a blood-red coloration. The reaction is still very distinct in a solution of 1 in 2000, and perceptible at a dilution of 1 in 50,000. The red coloration is destroyed by excess of mineral acids. The reaction is at once given by urine containing antipyrine.

On mixing cold aqueous solutions of antipyrine and mercuric

[1] The liquid filtered from the crystals gradually changes colour from green to brown, and after standing for some hours is found to smell of hydrocyanic acid, but the quantity of this body formed appears to be very minute (Wood and Marshall, *Pharm. Jour.*, [3], xix. 806).

chloride, a white precipitate is formed. On boiling the liquid this disappears, but on continued boiling a brown resinoid substance is deposited, which, when separated, is found to be soluble in hot alcohol and in nitric acid, and is coloured scarlet by strong sulphuric acid.

Antipyrine reacts in the general manner of alkaloids. Thus, in acid solutions it gives a yellowish-white precipitate with Mayer's reagent, and the same with Marmé's test (potassio-cadmium iodide); a green precipitate changing to orange-red with *potassio-iodide of bismuth*; an abundant reddish-yellow precipitate with Nessler's reagent; a white with phosphomolybdate of sodium; and an abundant white precipitate with tannin.[1]

According to the *German Pharmacopœia*, the solution of antipyrine in two parts of water should be neutral, free from acrid taste, and not changed by sulphuretted hydrogen water. A 2 per cent. solution should give a white precipitate with tannin; and on addition of two drops of fuming nitric acid to 2 c.c. of the solution, a green coloration should occur, *changed to red on boiling and adding another drop of nitric* acid. 2 c.c. of a 0·2 per cent. solution gives a deep red colour with a drop of ferric chloride solution, changed to bright yellow on adding 10 drops of sulphuric acid. Similar tests are given in the additions (1890) to the *British Pharmacopœia*, in which antipyrine receives the designation "phenazone."[2]

Antipyrine has now an established position and wide application in medicine. Although originally introduced as a febrifuge, it is taking a still higher place as an anodyne. Given in 10 to 20 grain doses in cases of bilious and nervous headache, it often effects a remarkably rapid and perfect cure. It has been usefully injected hypodermically in 8-grain doses as a substitute for morphia; and for the relief of pain in acute and chronic gout, neuralgia, sciatica, &c. The subcutaneous injection of antipyrine is said not to be followed by drowsiness, vomiting, or excitement. It is stated to be almost a specific in puerpural fever. It has been found valuable as a hæmostatic, and has proved successful in some cases of sea-sickness, but by no means invariably. Antipyrine causes an almost immediate re-

[1] The reactions described in the text sufficiently indicate the pharmaceutical preparations with which antipyrine is incompatible. Thus it should not be dispensed in a mixture with nitric acid, nitrites, chloral hydrate, solid sodium salicylate, carbolic acid, tannin, iodine, mercuric chloride, salts of iron, permanganates, or tinctures or infusions of catechu, cinchona, roses, galls, rhubarb, &c. (see Millard and Stark, *Pharm. Jour.*, [3], xx. 860).

[2] Antipyrine has been adulterated with acetanilide (see page 72).

duction in the temperature of the body (apparently from its influence on the brain-centres regulating the temperature), the effect continuing from four to six hours. It induces sweating and feeble pulse, and in excessive doses, or even small doses in certain cases, an eruption resembling nettle-rash, occasionally with vomiting and collapse.[1] Atropine has been found to act promptly as an antidote.

Antipyrine may be detected in the urine for eighteen to twenty-four hours after it is taken by the stomach, but can be detected only for a few hours in the different organs. It has been detected, after putrefaction for a fortnight, in animals killed within two hours after its administration, either by the stomach or hypodermically.

Antipyrine is readily extracted from animal matters, by rendering the liquid ammoniacal and agitating it with chloroform or amylic alcohol.

Antipyrine Salicylate, $C_{11}H_{12}N_2O, C_7H_6O_2$. If salicylic acid be gradually added to a dilute boiling solution of antipyrine, antipyrine salicylate separates as a yellowish oil. The compound can be more conveniently prepared by heating equivalent proportions of antipyrine and salicylic acid with a little water to 90°, or by shaking together an aqueous solution of antipyrine with an ethereal solution of salicylic acid, when the salt separates in fine crystals. Antipyrine salicylate melts at 89°–90° C., and decomposes at a somewhat higher temperature, dissolves in 250 parts of cold water, more freely in hot, and readily in alcohol, ether, chloroform, and carbon disulphide. The aqueous solution is faintly acid in reaction, and has a sweet taste and bitter after-taste. It gives a violet coloration with ferric chloride, and green with nitrous acid. Salicylate of antipyrine has been employed with favourable results in medicine under the name of "salipyrin." A mixture of antipyrine and salicylate of sodium gradually changes to an oily liquid on exposure to air. The change, which does not occur in a closed bottle, appears to be simply due to absorption of moisture by the salicylate and the solution of the antipyrine in the water thus absorbed.

Antipyrine becomes pasty when mixed with betanaphthol, and appears to form a compound with phenol. Under the name of "resopyrin," Portes has described a compound obtained by mixing solutions of molecular proportions of resorcinol and antipyrine. It crystallises in oblique rhombic prisms, insoluble in water but soluble in alcohol.

[1] The exhibition of antipyrine is unsafe when the heart is weak. A case where severe symptoms were produced by a dose of 1 gramme has been recorded by Schwabe (*Pharm. Jour.*, [3], xx. 1059).

Chloral-Antipyrine, $C_{11}H_{11}(C_2H_2Cl_3O)N_2O$. When dilute solutions of chloral hydrate and antipyrine are mixed no perceptible reaction occurs, but on concentrating the liquid, or on mixing strong solutions of the two substances, a separation of oily globules takes place, and these immediately or gradually change to a mass of crystals of chloral-antipyrine. The same substance may be obtained by heating molecular proportions of chloral hydrate (165·5 parts) and antipyrine (188 parts) to 110°–115° C. The reaction consists in elimination of water and substitution of the group $CCl_3.CH(OH)$ for one of the hydrogen atoms of the antipyrine;[1] but whether the replaced atom is one of those of the methyl groups, or the hydrogen atom of the CH group, is not definitely decided (compare *Pharm. Jour.*, [3], xx. page 862 with page 889).

Chloral-antipyrine, also called h y p n a l, crystallises from alcohol in hard scales and from water in transparent rhombs. It melts at 67°–68°, is almost odourless, and has a saline taste with an after-taste suggestive of chloral. It is only slightly soluble in cold alcohol, ether, and chloroform, but somewhat more soluble in boiling alcohol, and is dissolved by about eight parts of warm water. The solution reduces Fehling's solution on warming, gives the blood-red reaction of antipyrine with ferric chloride, and yields chloroform when heated with dilute caustic alkali. When chloral-antipyrine is kept in a melted state for some time, it deposits crystals of a *dehydration compound*, which is insoluble in water, melts at 186°–187°, and gives no colour-reaction with ferric chloride. According to R e u t e r (*Pharm. Jour.*, [3], xx. 602) chloral-antipyrine is physiologically inert, but B a r d e t found doses of 1 gramme to induce sleep as readily as chloral hydrate, while in cases of insomnia caused by pain it seemed to have the same anodyne effect as antipyrine. S c h m i d t finds the monochloral-derivative to have more decided soporific effect and a less deleterious influence on the circulation than antipyrine.

Bichloral-Antipyrine is obtained by heating antipyrine with excess of a strong solution of chloral hydrate, when an oily layer is formed, which solidifies to prismatic crystals melting at 67°–68°, soluble with some dissociation in ten parts of cold water, and giving the reactions of chloral-antipyrine.

[1] Butyl-chloral behaves similarly with antipyrine.

BASES FROM TAR.

The numerous constituents of tars may be roughly divided into—

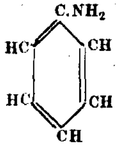
(*a*) Indifferent Bodies :—as Hydrocarbons ;

(*b*) Acid Bodies :—as Phenoloids and Acetic Acid ; and

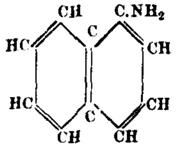
(*c*) Bases :—as Ammonia, Aniline, Pyridine, &c.

The principal members of the first two groups have already been considered at length. Ammonia is beyond the scope of present work, and the remaining bases which require consideration all belong to the aromatic group. They may be arranged in several groups, each one of which is represented by a typical member. Thus :—

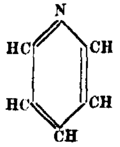
1. Aniline, or Amido-benzene, $C_6H_5.NH_2$, or .



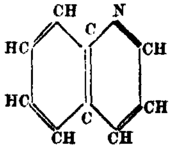
2. Naphthylamine, or Amido-naphthalene, $C_{10}H_7.NH_2$, or . . . .



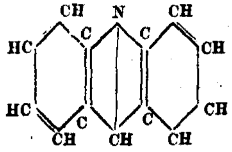
3. Pyridine, C_5H_5N, or . . . .



4. Quinoline, C_9H_7N, or . . . .



5. Acridine, $C_{13}H_9N$, or . . . . . .



From these formula it appears that the substitution of nitrogen is outside the ring in the case of aniline and naphthylamine. On the other hand, pyridine, quinoline, and acridine are derived from benzene, naphthalene, and anthracene respectively, by the substitution of N for one of the CH groups of the closed chain.

Naphthylamine does not appear actually to exist in coal-tar, and aniline occurs in tar in very limited quantity; these bases are obtained synthetically from constituents of coal-tar.

Besides the foregoing typical bases and their allies and derivatives, certain volatile bases (*e.g.*, piperidine, conine, nicotine), ordinarily prepared from plants, and therefore classed with other vegetable alkaloids, have a connection with pyridine or quinoline which is now fully demonstrated.

ANILINE AND ITS ALLIES.

Aniline is the type of a large number of organic compounds of synthetical origin.

Aniline has the constitution of a mono-amidobenzene or mono-phenylamine, and may be regarded as originating in the replacement of one of the hydrogen atoms of the benzene-ring by the group amidogen, NH_2; or one of the hydrogen atoms of ammonia by the radical phenyl, C_6H_5. Thus:—

$$C_6H_5.NH_2\text{, or } \left.\begin{matrix}(C_6H_5)\\H\\H\end{matrix}\right\}N$$

Aniline exists in minute quantity in coal-tar, but is ordinarily produced by nitrofying benzene, C_6H_6, and reducing the resultant nitrobenzene, $C_6H_5NO_2$, by nascent hydrogen.

If the treatment with nitric acid be carried further, dinitrobenzene, $C_6H_4(NO_2)_2$, is produced, and this by reduction is converted into meta-phenylene-diamine or meta-diamido-benzene, $C_6H_4(NH_2)_2$.

If the reduction of nitrobenzene be effected by alkaline reagents, two molecules coalesce, and azobenzene, $C_6H_5.N:N.C_6H_5$, is produced. On further treatment of this (especially in alcoholic solution) it is converted into hydrazobenzene, $C_6H_5.NH.NH.C_6H_5$, which by intramolecular change is transformed into benzidine or di-para-amido-diphenyl, $NH_2.C_6H_4.C_6H_4.NH_2$. The relationship of aniline to the allied bases[1] is shown below:—

[1] Hydrazobenzene has no basic properties.

Aniline (Amidobenzene).	*Aniline.*	*Aniline* (Phenylamine).
$NH_2.C_6H_4.H$	$C_6H_5.NH.H$	$C_6H_5.NH.H$
Phenylene-diamine.	*Phenylhydrazine.*	*Diphenylamine.*
$NH_2.C_6H_4.NH_2$	$C_6H_5.NH.NH_2$	$C_6H_5.NH.C_6H_5$
Benzidine.	*Hydrazobenzene.*[1]	*Hydrazobenzene.*[1]
$NH_2.C_6H_4.C_6H_4.NH_2$	$C_6H_5.NH.NH.C_6H_5$	$C_6H_5.NH.NH.C_6H_5$

Aniline forms two classes of homologues. The true homologues (Class A) coexist with aniline in coal-tar, and are derived from aniline by the substitution of one or more methyl groups for a corresponding number of the hydrogen atoms of the benzene nucleus. They are ordinarily obtained by nitrofying the corresponding hydrocarbons prepared from coal-tar naphtha, and reducing the resultant nitro-derivatives. Thus :—

Hydrocarbon.	*Nitro-derivative.*	*Amido-derivative.*
Benzene— $C_6H_5.H$	Nitrobenzene— $C_6H_5.NO_2$	Aniline— $C_6H_5.NH_2$
Toluene— $C_6H_4(CH_3).H$	Nitrotoluene— $C_6H_4(CH_3).NO_2$	Toluidine— $C_6H_4(CH_3).NH_2$
Xylene— $C_6H_3(CH_3)_2.H$	Nitroxylene— $C_6H_3(CH_3)_2.NO_2$	Xylidine— $C_6H_3(CH_3)_2.NH_2$
Cumene— $C_6H_2(CH_3)_3.H$	Nitrocumene— $C_6H_2(CH_3)_3.NO_2$	Cumidine— $C_6H_2(CH_3)_3.NH_2$

Isomeric modifications are known of all the members of the series except those in the first line (page 51 *et seq.*).

The pseudo-homologues of aniline (Class B) are derived from aniline by the replacement of one or both of the hydrogen atoms of the amido-group by methyl or other alkyl radical. Similar substitutions can be effected in the amido-groups of toluidine, xylidine, &c.

These alkylated anilines (Class B) are obtained by the action of methyl chloride or other alkyl salt on aniline, or of the corresponding alcohol on the hydrochloride or other salt of aniline (see page 73). Paratoluidine has also been obtained in a very interesting manner by heating the hydrochloride of methyl-aniline[2] to 350° C. in a sealed tube, when change of position of the atoms within the molecule takes place thus :—

$$\left.\begin{matrix} C_6H_5 \\ CH_3 \\ H \end{matrix}\right\} N = \left.\begin{matrix} C_6H_4(CH_3) \\ H \\ H \end{matrix}\right\} N$$

Methyl-aniline. Para-toluidine.

[1] Hydrazobenzene has no basic properties.

[2] If the hydriodide of methyl-aniline be similarly treated, ortho- or meta-toluidine is obtained.

By the same process methyl-toluidine may be converted into xylidine, and this by consecutive steps into a pseudo-cumidine, isoduridine, and amido-pentamethylbenzene (page 60). By treating aniline hydrochloride with aniline, diphenylamine or phenylaniline, $C_6H_5.NH(C_6H_5)$, is obtained[1] (page 79).

Substitution of the hydrogen atoms of aniline and its homologues can also be effected by acid or chlorous groups, both in the benzene-nucleus and in the amido-group. In the latter case the derivatives are called anilides (page 67), and are quite different from the bodies resulting from the substitution of chlorous radicals for the benzenic hydrogen. In the compounds of the latter class, the basic character is either much weakened or entirely destroyed. Most of the derivatives exist in several isomeric modifications, according to the position of the substituting radicals in the benzene-nucleus. Examples of the bodies of this class are :—

Aniline-sulphonic acid or sulphanilic acid, $C_6H_4(SO_3H).NH_2$ (page 49).
Nitraniline, $C_6H_4(NO_2).NH_2$ (page 50).
Bromaniline, $C_6H_4Br.NH_2$.
Trichloraniline, $C_6H_2Cl_3.NH_2$.

Mixed substitution-products, belonging at once to two or more of the foregoing classes, are obtainable by suitable means. As examples may be mentioned :—

Paranitracetanilide, ... $C_6H_4(NO_2).NH(C_2H_3O)$
Paranitroso-dimethylaniline, . . $C_6H_4(NO).N(CH_3)_2$
Paranitroso-dimethyl-paratoluidine, $C_6H_3(CH_3)(NO).N(CH_3)_2$

The more important of the allies and derivatives of aniline formulated on this and the preceding pages are described in greater detail in the sequel.

On treating aniline, and also many of the above-mentioned homologues and derivatives, with oxidising agents, a series of brilliant colouring matters are obtained, which form the well-known "aniline dyes" (Part I. page 214 *et seq.*).

By the action of nitrous acid, or a nitrite, on a cold solution of a salt of aniline a salt of diazobenzene is obtained. This and the allied products obtained by similar means from the homologues and analogues of aniline form the starting-point of the numerous and important colouring matters known as the "azo-dyes" (Part I. page 175 *et seq.*).

[1] Diphenylamine and aniline hydrochloride cannot be caused to react with formation of triphenylamine, $(C_6H_5)_3N$; but this body can be obtained by the action of mono-brombenzene on di-potassium aniline :—

$$2C_6H_5Br + C_6H_5.NK_2 = (C_6H_5)_3N + 2KBr.$$

By the action of reducing agents on the salts of diazobenzene, phenylhydrazine, $C_6H_5NH(NH_2)$, is obtained. The body has already been fully described (page 27).

Aniline.[1] Amidobenzene. Phenylamine.

$$C_6H_7N = C_6H_5.NH_2 = \left.\begin{matrix} C_6H_5 \\ H \\ H \end{matrix}\right\} N$$

Aniline occurs to a limited extent ready-formed in the products of the distillation of coal, bone, and peat. Of late years a small quantity has been actually recovered from coal-tar naphtha, but almost the whole of it is obtained indirectly from coal-tar by the action of a reducing agent on nitrobenzene ("Aniline Oils," page 60). Aniline may also be obtained by passing ammonia and benzene vapour through a red-hot tube:—$C_6H_6 + NH_3 = H_2 + C_6H_7N$. It is also formed together with diphenylamine by the reaction of phenol and ammonia. The best yield is obtained by heating phenol to about 330° for twenty hours with ammonium chloride and magnesia or oxide of zinc (or ammonio-zinc chloride, $Zn(NH_3)_2Cl_2$). Aniline is also obtained by numerous other reactions.

Aniline may be purified by fractional distillation and conversion into the acetyl-derivative. This is recrystallised from water, and on saponification yields pure aniline.

Pure aniline is a colourless, oily liquid, of faintly vinous odour and aromatic, burning taste. It refracts light strongly, but has no rotatory action. Aniline, when very pure, freezes at 8° C., but a slight admixture greatly reduces its solidifying point. It boils at 183°–184° C., and distils unchanged.

The specific gravity of aniline is 1·0379 at 0° and 1·0216 at 20°, compared with water at 4°; and 1·0242 at 15°, compared with water at the same temperature. The coefficient of expansion is ·000818.

Aniline becomes yellow or brown on exposure to air and light, especially at elevated temperatures, a resinous body being ulti-

[1] Aniline was first obtained in 1826 by Unverdorben by the dry distillation of indigo, and received the name *crystalline*. Runge in 1834 obtained it from coal-tar, and termed it *kyanol*. The name *aniline* is due to Fritsche, who in 1841 obtained it by distilling indigo with caustic alkali. The name *benzidam* was given it in 1842 by Zinin, who prepared it by reducing nitrobenzene by sulphuretted hydrogen. The name *phenamide* has also been proposed for it. Aniline was first accurately described in 1843 by A. W. Hofmann.

mately formed. The change is due to oxidation, and does not occur *in vacuo* or in the dark.[1]

Aniline is only slightly soluble in water, requiring 31 parts at the ordinary temperature, but being more soluble in hot water. Water also dissolves in aniline, 5 parts being taken up by 100 of aniline at the ordinary temperature, and somewhat more at higher temperatures. The greater part can be separated by distillation, the water passing over first, but the last traces can only be removed by prolonged digestion over caustic alkali.

Aniline is soluble in all proportions in a 50 per cent. aqueous solution of its hydrochloride, and in smaller proportions in more dilute solutions (see page 67).

Aniline dissolves readily in alcohol, ether, wood-spirit, acetone, chloroform, carbon disulphide, and volatile hydrocarbons.

Aniline is itself a solvent for sulphur, phosphorus, indigotin, camphor and colophony, but does not dissolve caoutchouc or copal. It is employed sometimes as a solvent for aniline-blue.

Aniline is a powerful poison, coagulating albumin and producing symptoms similar to those caused by nitrobenzene (Vol. II. page 478).[2]

Aniline has marked basic properties, a long series of well-defined and crystallisable salts being obtained from it. It has, however, no action on phenol-phthaleïn, litmus or turmeric, though it affects a few of the more delicate vegetable colours. It expels ammonia from its salts at a boiling temperature, but is itself displaced in the cold. Aniline decomposes the solutions of many metallic salts, with precipitation of the corresponding hydroxides. When heated with strong sulphuric acid, aniline is converted into para-amido-benzene-sulphonic acid (sulphanilic acid). With hot fuming sulphuric acid, a di-sulphonic acid is produced.

[1] According to A. Bidet (*Compt. Rend.*, cviii. 520; *Jour. Soc. Chem. Ind.*, viii. 383), aniline and toluidine prepared by the reduction of pure nitro-derivatives are colourless after distillation, and though they become yellowish in a few days, light has no further effect on them, and even this change Bidet attributes to the presence of amido-thiophene, $C_4H_3S.NH_2$.

[2] According to Letheby and Turnbull the action of aniline is chiefly on the nervous system. According to Grandhomme, the first symptom in slight cases of poisoning by aniline, caused by inhaling the vapour, is a blue colour on the edge of the lips, while the gait becomes unsteady, the speech thick, the head affected, and the face pale, while the appetite fails completely. Alcohol aggravates the symptoms. In more severe cases, such as may arise from the saturation of the clothes with aniline, the lips become dark blue or black, and the vertigo is so violent that standing becomes impossible. According to Wöhler and Frerichs, aniline does not exert any poisonous action on dogs. Runge found the aqueous solution to kill leeches and the parts of plants immersed in it.

In presence of an excess of acid, aniline imparts a deep yellow colour to pine-wood and alder-pith.

According to Friswell, on adding cupric sulphate to an aqueous solution of aniline an apple-green crystalline precipitate is formed; or in extremely diluted solutions a green coloration.

Cold aqueous solutions of aniline salts are converted by treatment with nitrous acid (or a nitrite and mineral acid) into salts of diazobenzene. On boiling the solution phenol is formed, with evolution of nitrogen.

Under the influence of oxidising agents aniline gives products and reactions which vary considerably according to the oxidiser employed, thus:—

a. When aniline is treated with excess of nitric acid, and the mixture evaporated at 100° C., the base is decomposed with formation of a brown substance. With smaller proportions of nitric acid various coloured products are formed, including picric acid.

b. When treated with dilute sulphuric acid and manganese dioxide, aniline yields ammonia and quinone, $C_6H_4O_2$, but the greater part of the product undergoes still further change.

c. If aniline be dissolved in strong sulphuric acid, and a few drops of a solution of potassium bichromate be added, a red colour is produced, which rapidly changes to deep blue.

d. On treating aniline, or one of its salts in a solid state, with strong sulphuric acid, and then adding a minute fragment of manganese dioxide or other oxidising agent (in the manner described under "strychnine"), a fine purple coloration is produced. A better result is obtainable by employing electrolytic oxygen; in this form the test is the most delicate and satisfactory which can be applied.

e. Chlorine acts on dry aniline with great violence, producing a black mass containing trichloraniline, $C_6H_4Cl_3N$. Bromine behaves similarly; and, on adding bromine-water to the aqueous solution of an aniline salt, a precipitate of tribromaniline is formed. On the other hand, Mills and Muter (*Jour. Soc. Chem. Ind.*, iv. 96) state that aniline in solution in carbon disulphide reacts with Br_2, probably forming an additive compound.

f. When a solution of aniline is treated with a dilute solution of bleaching powder, avoiding excess, a fine purple coloration results, which gradually changes to brown. When carefully applied, the reaction is delicate and characteristic. The colour is destroyed by ether.

g. If a minute quantity of aniline be treated with an aqueous solution of phenol, and a solution of bleaching powder be then gradually added, the reagent produces yellow striæ, which change

to a greenish-blue. The test, which is due to Jacquemin, is said to be very delicate.

h. If aniline, or one of its salts in the solid state, be treated with a drop of chloroform, and then solid potash or a strong solution of potash in alcohol be added, and the whole gently heated by immersing the tube in hot water, a peculiar and highly unpleasant odour will be produced, due to the formation of phenyl-carbamine, $C_6H_5.NC$. The reaction, which is known as "Hofmann's isonitrile test," is produced by other aromatic monamines, and by acetanilide.

Detection and Separation of Aniline.

The foregoing colour-reactions are amply sufficient for the recognition of aniline, provided that a proper process of separation be previously applied.

Aniline may be liberated from the aqueous solutions of its salts by addition of caustic soda, and may then be extracted by agitating the liquid with ether. On separating the ethereal layer, and agitating it with dilute hydrochloric acid, the aniline passes into the aqueous liquid, which may then be concentrated or evaporated to dryness, and examined by the colour-reactions already described. From strychnine, which is the only substance with which aniline is at all apt to be confounded, it may be separated by adding caustic soda to the concentrated solution, and distilling over the aniline by driving in a current of steam. The strychnine remains in the flask, while the aniline will be found in the distillate if it be acidulated with hydrochloric acid and concentrated to a small bulk at 100° C. The same plan may be employed for detecting aniline in toxicological inquiries, or the process used for isolating strychnine may be used, but instead of evaporating the ether-chloroform it should be separated and agitated with dilute hydrochloric acid in the manner above described.

F. Müller (*Jour. Chem. Soc.*, lii. 514) found unchanged aniline in the urine of a person poisoned with it. The urine was optically inactive, but reduced Fehling's solution. A portion of the concentrated urine, when boiled with strong hydrochloric acid, neutralised with soda, and extracted with ether, gave an ethereal solution which showed the blue indophenol reaction. The ethereal extract of the unboiled urine did not give this reaction, a fact which Müller believes was due to the secretion of the aniline as para-amidophenylsulphate (compare "Phenyl-Sulphuric Acid," Part I. page 9); a substance which is split up by boiling with hydrochloric acid. In support of this, the original urine contained sulphates (estimated by barium chloride),

equivalent to only 0·0475 gramme of sulphuric acid per litre; but after boiling with hydrochloric acid, 0·8085 gramme. A direct test for the presence of paramidophenylsulphates in urine consists in boiling the liquid with one-fourth of its measure of strong hydrochloric acid, adding a few c.c. of a 3 per cent. solution of phenol, and then some drops of a chromic acid solution. If para-amidophenol be present, the liquid becomes red, and turns blue on adding ammonia.

The *determination* of aniline may be effected by evaporating its ethereal solution, or preferably by extracting the base therefrom by agitation with dilute hydrochloric acid, evaporating the acid liquid, and weighing the residual hydrochloride. Under favourable circumstances it may be measured after liberation from a strong solution of the hydrochloride by addition of caustic alkali.

Instead of weighing the aniline hydrochloride, the salt may be redissolved in water, and the solution titrated with standard silver nitrate. Or it may be titrated with standard caustic alkali and phenolphthaleïn or litmus, as aniline hydrochloride acts on these indicators exactly like an equivalent quantity of free hydrochloric acid, and the end-reaction is perfectly sharp. The process allows of the titration of aniline in presence of neutral ammoniacal salts. On the other hand, with helianthin (methyl-orange), the basic character of free aniline is distinctly marked, but the end-reaction is not sufficiently definite to render the indicator available for accurately titrating aniline.

According to Julius (*Jour. Soc. Dyers, &c.*, ii. 79), free aniline in aqueous solution can be satisfactorily titrated with standard sulphuric or hydrochloric acid, if congo-red be employed as an indicator and the neutral point be regarded as that at which a bluish-violet colour is obtained, not changed by further small additions of acid; but a much larger excess is required to produce a pure blue. Results are said to be obtainable agreeing within 0·2 per cent. with theory.

SALTS OF ANILINE.

Aniline combines readily with acids forming a series of salts which crystallise well. The following are the most important.

Aniline Hydrochloride. Hydrochlorate of Aniline. C_6H_7N,HCl. This salt crystallises with great facility in colourless needles, or large plates, which are very soluble in water and alcohol. It melts at 192° C., and may be sublimed unchanged. It yields double salts with stannic, mercuric, antimonious, platinic, and auric chlorides; *aniline chloroplatinate*, $(C_6H_7N,HCl)_2PtCl_4$, crystallises from hot water in yellow needles. *Aniline salt* is

the ordinary commercial name for aniline hydrochloride. It is manufactured by mixing the calculated weights of aniline and hydrochloric acid in stone-tanks, freeing the crystals formed from the mother-liquor by a centrifugal machine, and drying them. According to another process, aniline is dissolved in petroleum spirit of 0·720 specific gravity, and hydrochloric acid gas passed in till the solution is saturated. The aniline salt is deposited as a white powder, which is separated from the adhering petroleum spirit by hydraulic pressure, and ground to powder.

Aniline salt is employed largely in calico-printing, its chief use being for the production of *aniline-black* (Part I. page 250). It is important that the salt intended for this purpose should be made from pure aniline, and should be dry and neutral. The presence of free acid in the aniline salts is liable to cause the cloth dyed black to rot in the steaming process. It must be free from sand or grit, which would injure the printing rollers, and will produce streaks on the printed cloth. *Grit* remains undissolved when the sample is treated with hot water, and may be filtered off, dried or ignited, and weighed. Free acid is best determined by titration with decinormal caustic alkali, using methyl-orange as an indicator, but the results are not very satisfactory. A useful method of examination consists in titrating the aqueous solution of 2 grammes of the sample with normal caustic soda, using litmus or phenolphthaleïn as an indicator. The amount neutralised corresponds to the total acid, both free and combined with aniline. Theoretically, 2 grammes of pure aniline hydrochloride would require 15·4 c.c. of normal caustic soda, but owing to the presence of toluidine and moisture commercial samples of good quality require between 14 and 15 c.c.[1] The process will indicate the presence of ammonium chloride, which will not neutralise alkali, and hence a sample containing it will require a less volume of the standard solution. *Ammonium chloride* is occasionally met with in considerable proportion as an adulterant of aniline salts. For its accurate determination the sample should be dissolved in water, excess of caustic soda added, the liberated aniline separated, and the aqueous solution distilled in the usual way. On titrating the distillate with standard acid and litmus or phenolphthaleïn, only the ammonia will be indicated. *Fixed impurities* will be detected on igniting the sample; a mere trace should be present. An idea

[1] This method of examining aniline salts is due to R. Williams (*Chem. News*, l. 299), but he appears to attribute the reaction to the presence of free acid.

of the proportion of *toluidine* present in the sample can be obtained by liberating the mixed bases from the solution of the salts by caustic soda, and heating a few centimetres of the aniline with an equal quantity of strong arsenic acid solution to 180° C. for some time. On boiling the product with water, the intensity of the crimson coloration will increase with the proportion of toluidine in the sample. A more accurate result can be obtained in the manner indicated on page 64.

Aniline Sulphate, $(C_6H_7N)_2H_2SO_4$. This salt forms a crystalline powder, which is readily soluble in water and slightly so in alcohol. It is insoluble in ether, a fact which distinguishes it from the sulphate of methylamine.

Aniline Oxalate, $(C_6H_7N)_2H_2C_2O_4$, is very slightly soluble in cold water or alcohol, and insoluble in ether.

Aniline Acetate, $C_6H_7N,HC_2H_3O_2$, does not appear to have been obtained in a crystalline form. When heated it loses the elements of water and forms acetanilide (see page 68).

ANILINE-SULPHONIC ACIDS. AMIDOBENZENE-SULPHONIC ACIDS. When aniline is treated with an equivalent amount of dilute or concentrated sulphuric acid it is converted into aniline sulphate. If an excess of acid be used, a high temperature employed, or sulphuric anhydride be present, aniline-sulphonic acid is produced:—

$$C_6H_5.NH_2 + SO_2(OH)_2 = C_6H_4\begin{cases} SO_2.OH \\ NH_2 \end{cases} + H.OH$$

Three modifications of this body exist, which differ according to the relative positions of the NH_2 and SO_3H groups in the benzene-chain. The ortho-sulphonic acid (1:2) has no practical interest, but the meta- and para-acids are manufactured on a large scale for the production of aniline- and azo-dyes.

Meta-amidobenzenesulphonic Acid, $C_6H_4(NH_2)^{(1)}.SO_3H^{(3)}$, is employed for the manufacture of *metanile-yellow* (Part I. page 190). It is prepared by warming nitrobenzene with fuming sulphuric acid, or by treating a solution of benzene in strong sulphuric acid with fuming nitric acid, when a mixture of nitro-benzenesulphonic acids, $C_6H_4(NO_2)SO_3H$, is obtained, in which the meta-acid predominates, and may be roughly separated from its isomers by conversion into the barium or calcium salt. The meta-nitro-sulphonic acid yields, on reduction, the corresponding amido-sulphonic acid.

Para-amidobenzenesulphonic Acid, $C_6H_4(NH_2)^{(1)}.SO_3H^{(4)}$, likewise called *Sulphanilic Acid*, is prepared on a large scale by heating one part of aniline and three of concentrated sulphuric acid to 195°. With fuming acid, the reaction occurs more rapidly and at a

lower temperature. On pouring the cooled product into water, the acid separates as a crystalline mass, which can be recrystallised from hot water.

Sulphanilic acid crystallises in rhombic tables containing 1 aqua, which effloresce in the air, and are only slightly soluble in cold, but readily in hot, water. Treatment with potassium bichromate and sulphuric acid oxidises it to quinone, $C_6H_4O_2$. The solution of the sodium salt, on treatment with sodium nitrite, yields sodium diazobenzenesulphonate (Part I. page 177). Aniline sulphanilate gives off all its base at 100°.

NITRANILINES. When aniline is treated with dilute nitric acid it yields aniline nitrate. With the concentrated acid it reacts far more violently than benzene, and is converted into quinone and other products. To obtain a nitro-derivative by such means, the aniline must be protected by employing its acetyl-derivative, or by nitrofying in presence of excess of strong sulphuric acid. In the latter case a mixture of the three isomeric nitranilines is obtained, but chiefly the *meta*-compound; in the former case *para*-nitracetanilide, $C_6H_4(NO_2).NH(C_2H_3O)$, is formed, together with some of the *ortho*-compound, both of which readily yield the corresponding nitraniline, $C_6H_4(NO_2).NH_2$, on boiling with concentrated hydrochloric acid or caustic alkali.

Another method of preparing the nitranilines, especially the *meta*-modification, is the reduction of the corresponding dinitrobenzenes in alkaline alcoholic solution. Under these circumstances only one of the NO_2 groups is reduced to NH_2, whereas in acid solutions diamidobenzene, $C_6H_4:(NH_2)_2$, is obtained (page 86).

	NITRANILINES, $C_6H_4(NO_2).NH_2$.		
	Ortho. $NO_2:NH_2=1:2$	*Meta.* $NO_2:NH_2=1:3$	*Para.* $NO_2:NH_2=1:4$
Appearance and Crystalline form.	Orange-yellow needles.	Long yellow needles.	Long yellow needles.
Taste, ...	...	Sweet, burning.	Nearly tasteless.
Melting-point, . .	71°	114°	147°
Volatility, . . .	Distils in a current of steam.	Sublimes at 100°. Distils in a current of steam.	Not volatile with steam.
Salts, ...	Very unstable.	Fairly stable.	Unstable.
Behaviour when boiled with strong soda,	...	Unchanged.	Forms para-nitrophenol—$C_6H_4(NO_2).OH$

The nitranilines are yellow crystalline bodies, readily soluble in alcohol but only slightly so in water. They are weak bases form-

ing yellow salts, and yield the corresponding diamidobenzenes on reduction. The preceding table exhibits their chief differences.

Two *dinitranilines*, $C_6H_3(NO_2)_2.NH_2$, are known, melting respectively at 182° or 138°. Also a *trinitraniline*, $C_6H_2(NO_2)_3.NH_2$, or picramide, which melts at 186°, and is converted into picric acid, $C_6H_2(NO_2)_3.OH$, and ammonia when boiled with caustic alkali.

Homologues of Aniline.

As already stated, the true homologues of aniline are bodies in which one or more atoms of the hydrogen of the benzene-nucleus are replaced by a corresponding number of atoms of methyl or other alkyl radical. The compounds in question may be prepared, and are produced commercially, by processes exactly similar to those which result in the formation of aniline. That is, the hydrocarbons toluene, xylene, &c., are treated with nitric acid, and the resultant nitro-derivatives are reduced to the bases by nascent hydrogen (usually iron and hydrochloric acid).

In their general chemical relationships the homologues present the closest resemblance to aniline, and yield substitution-products of a strictly parallel character. They are also diazotised similarly.

The only homologues of aniline which require separate description are the toluidines, C_7H_9N, and the xylidines, $C_8H_{11}N$. Their consideration will be followed by a section describing "aniline oils," under which term is included commercially pure aniline and toluidine, and various mixtures of these bases.

Toluidines. Amidotoluenes. Amido-methylbenzenes. Tolylamines.

$$C_7H_9N = C_7H_7.NH_2 = \left.\begin{matrix} C_6H_4(CH_3) \\ H \\ H \end{matrix}\right\} N$$

The toluidines exist in small quantity together with aniline in coal-tar. They are produced commercially from toluene by processes exactly analogous to those by which aniline is prepared from benzene, and together with aniline constitute nearly the whole of the "aniline oils" of commerce (page 60). An interesting method of producing toluidine is mentioned on page 41.

Three isomeric modifications of toluidine are known. The chief physical differences between them are shown in the following table, in which they are also contrasted with aniline and their metameride benzylamine, $C_6H_5.CH_2NH_2$.[1]

[1] Benzylamine is a colourless liquid of faint aromatic odour, and is not affected by light. It is miscible in all proportions with water, alcohol and

	Aniline.	*Ortho-toluidine.* $CH_3:NH_2=1:2$	*Meta-toluidine.* $CH_3:NH_2=1:3$	*Para-toluidine.* $CH_3:NH_2=1:4$	*Benzylamine.*
Specific gravity at 15°, . . .	1·0208	1·0037	0·998 (at 25°)	Solid.	·990
Melting-point, .	Solidifies at −8° C.	Does not solidify at −20°	Does not solidify at −13°	Melts at +45°	Liquid.
Boiling-point, .	183°·7	199°	197°	198°	185°
Characters of the acetyl-derivative:—					
Melting-point,	114°	107°	65°–66°	147°	57°–61°
Boiling-point,	295°	296°	302°–304°	307°	300°
1000 parts of water dissolve,	3·4 at 14°	8·6 parts at 19°	4·4 parts at 13°	0·89 at 22°	Soluble.
Solubility of the acid oxalate:—					
In 1000 parts of water at 15°,	...	23·8	20·5	8·7	...
In 1000 parts of ether at 15°,	...	0·50	Very slight.	0·016	...

Ortho-toluidine is formed by the reduction of ortho-nitrotoluene. It is a colourless liquid, turning brown on exposure to air or light, and otherwise closely resembling aniline. It differs from its isomerides by giving a green coloration when treated with ferric chloride and a little para-diamidobenzene. A solution of 1 in 10,000 gives a fairly deep coloration, and one of 1 in 100,000 assumes a distinct greenish tint. All commercial aniline gives this reaction, and even that prepared by the distillation of indigo with caustic alkali.

Meta-toluidine is produced by the reduction of meta-nitrotoluene, preferably by an acid solution of stannous chloride. It is only present in small proportion in commercial toluidine. For its detection and approximate determination the mixed bases are converted into hydrochlorides, and the greater part of the isomeric salts removed by fractional crystallisation. The mother-liquor is evaporated to dryness, and the residue heated with methyl alcohol to 200°, under pressure, for a considerable time. This produces a mixture of the three isomeric dimethyl-toluidines,

ether, but is separated from its aqueous solutions by caustic alkalies (compare "Pyridine"). It has a strongly alkaline reaction, fumes with hydrochloric acid, and absorbs carbon dioxide from the air, with conversion into silky needles of the *carbonate*.

but only the meta-modification yields a nitroso-derivative, $C_6H_3(NO)(CH_3).N(CH_3)_2$, on adding sodium nitrite to an ice-cold solution of its hydrochloride. The hydrochloride of nitroso-dimethylmetatoluidine thus prepared, crystallises from a hot acidulated solution in greenish-yellow needles only slightly soluble in cold water. On treatment with sodium carbonate the free base is obtained, melting at 92°, crystallising from water or ether in small green plates or long needles, and precipitated in moss-green needles on adding petroleum ether to its chloroformic solution. All its solutions have a deep green colour. Nitroso-dimethylmetatoluidine forms steel-blue compounds with aniline and orthotoluidine.

According to Rosenstiehl, the three modifications of toluidine may be distinguished by the following reactions:—

	Orthotoluidine.	*Metatoluidine.*	*Paratoluidine.*
1. To a solution of the base in sulphuric acid, of 1·75 sp. gr., add a solution of chromic acid in sulphuric acid of the same strength.	Blue coloration changing on dilution to a permanent red-violet.	Yellow-brown coloration, becoming greenish-yellow on slight dilution, and colourless on further addition of water.	Yellow coloration.
2. To a solution of the base in sulphuric acid of 1·75 sp. gr., add nitric acid.	Orange coloration, or in very concentrated solutions, brown, becoming yellow on dilution.	At first red, rapidly changing to intense blood-red, and then dirty red; on dilution, orange.	Blue streaks which soon tinge the whole liquid; (in presence of aniline or orthotoluidine, blood red). The colour quickly becomes violet, then red, and, after some hours, brown.
3. Dissolve the base in ether, and add an equal volume of water. Then add a few drops of clear solution of bleaching powder.	The aqueous layer becomes first yellow and then brown. The ethereal layer, after separation, gives a permanent reddish-violet coloration with dilute sulphuric acid.	The aqueous layer becomes a thick brownish-yellow. The ethereal layer becomes reddish, and after separation and addition of dilute sulphuric acid is coloured violet at the under-surface.	No reaction. In presence of aniline the ether becomes blue on agitation.

Para-toluidine is produced by the reduction of the nitrotoluene derived from the toluene produced by the dry distillation of Tolu balsam; also by heating paracresol to 300° with ammonia and chloride of zinc; and by molecular transposition from methylaniline hydrochloride (page 41). It crystallises from hot

dilute alcohol in colourless plates melting at 45°, and has a peculiar odour recalling that of aniline.

Commercial Toluidine consists chiefly of a mixture of the ortho- and para- modifications. According to Friswell, the specific gravity of the *orthotoluidine* of commerce should be about 1·0037, and its boiling-point from 197° to 198° C. It ought not to solidify on cooling to −4°, though the majority of samples contain sufficient paratoluidine to cause them to commence crystallising at this temperature. The *paratoluidine* of commerce occurs in white dry crystals, melts at 43°–45°, and distils between 196° and 198°. *Liquid* commercial toluidine should boil at 197°–198°, have a specific gravity of about 1·000, and contain from 30 to 40 per cent. of paratoluidine and 60 to 70 of orthotoluidine.

A portion of the para-modification separates from the commercial mixture of the isomers when the liquid is cooled by a freezing mixture. A further separation is effected in practice by fractionally saturating the mixture of the bases with sulphuric acid, and then distilling in a current of steam. Orthotoluidine being a weaker base than the para-compound, the former will alone pass into the distillate if the quantity of sulphuric acid employed be somewhat in excess of that requisite to neutralise the paratoluidine.

L. Lewy (*Jour. Chem. Soc.*, l. 872; *Jour. Soc. Chem. Ind.*, v. 481) has proposed to separate ortho- and para-toluidine by converting the bases into phosphates. It appears that when paratoluidine and orthophosphoric acid are brought together, *di*-toluidine orthophosphate, $(C_7H_9N)_2H_3PO_4$, is produced as a salt crystallising in scales and very sparingly soluble in cold water, but more readily, with partial dissociation, in boiling water. Aniline acts similarly, forming a sparingly soluble *di*-aniline orthophosphate, $(C_6H_7N)_2H_3PO_4$. On the other hand, orthotoluidine forms a *mono*-toluidine orthophosphate, $(C_7H_9N)H_3PO_4$, and never a di- or tri- salt. Hence in the phosphates obtained from a mixture of the two toluidines the proportions of the bases might be deduced from the percentage of phosphoric acid. The mono-orthotoluidine phosphate is more readily soluble in water than diparatoluidine or dianiline phosphate. Further, when its solution is shaken with free aniline or paratoluidine, the orthotoluidine is set free. Hence pure orthotoluidine can be obtained from commercial toluidine[1] by adding rather more of a 21 per cent. aqueous solution of phosphoric acid than will suffice to form diphosphates

[1] The xylidines and cumidines behave like orthotoluidine, and form only monophosphates.

with the aniline and paratoluidine present. On warming the liquid, the free orthotoluidine forms a layer at the surface, which may be separated and distilled. The process may be modified by adding a further quantity of phosphate to convert the orthotoluidine into monophosphate, and then cooling the liquid and allowing it to stand to secure the complete deposition of the paratoluidine phosphate.

Wölfing (*Ber.*, xix. 2132) states that orthotoluidine prepared by Lewy himself by the above process, both on the small and large scale, still contained as much as 4 per cent. of paratoluidine. For the preparation of pure paratoluidine he recommends (*Dingl. Polyt. Jour.*, cclxiii. 260) that the hydrochlorides of the bases should be treated with an amount of sodium nitrite only sufficient to convert the orthotoluidine present into amidoazotoluene. Only when this change is complete does the paratoluidine react with the nitrite to form a diazo-amido-compound.

A method of determining the proportions of the ortho- and para-modifications of toluidine in the commercial product has been based by Rosenstiehl on the different solubilities of the acid oxalates of the two bases. The acid oxalate of paratoluidine requires 6660 parts of ether for solution, while the corresponding salt of orthotoluidine dissolves in 200 parts of ether. The method, somewhat modified, is as follows:—0·2 gramme of the sample is dissolved in 80 c.c. of anhydrous ether free from alcohol; 1·059 gramme of anhydrous oxalic acid, or 1·177 gramme of the crystallised acid, is dissolved in 250 c.c. of anhydrous, alcohol-free ether. Each c.c. of this solution will precipitate 0·005 gramme of toluidine. An excess is added to the ethereal solution of the sample, the liquid allowed to stand in a stoppered bottle for twelve hours, then filtered through paper, and the precipitate washed with ether. The precipitate is then washed into the bottle with water, and the solution titrated with decinormal caustic alkali and phenolphthaleïn. 1 c.c. of decinormal alkali represents 0·00535 gramme of paratoluidine. Miniati, Booth, and Cohen (*Jour. Soc. Chem. Ind.*, vi. 419) find that if too long a time be allowed for the precipitation, the product is liable to contain the orthotoluidine oxalate, and hence the result will be above the truth. They recommend that a repetition of the experiment should be made, in which the amount of oxalic acid solution used is only that requisite to combine with the paratoluidine found by the first test, so reducing the error to a minimum.

G. Lunge (*Chemische Ind.*, viii. 74; *Jour. Soc. Dyers, &c.*, i. 150) estimates the proportion of para- and ortho-toluidine in a

mixture of the two by a careful observation of the specific gravity. The determination is made by the bottle, and referred to water at 15° C. If the sample does not contain more than 50 per cent. of paratoluidine it is liquid at 15°, and consequently the observation is made at that temperature. With 50 to 60 per cent. of paratoluidine the method is still available if the bottle be filled at 20° C.; but with still larger proportions the results are unreliable, as the correction for temperature loses in accuracy, and the differences in specific gravity become very small for considerable alterations in the composition of the mixture. It is very desirable to adhere rigidly to the prescribed temperature, as an error of 1° C. causes an error of 7 per cent. in the estimation. The correction is ± 0·0008 for 1°, when the density is above 1·0008, and ± 0·0007 when below that point. All water must be removed by treating the sample with powdered caustic potash and redistilling. The distillation also serves to show the presence of aniline or xylidine, in presence of notable quantities of which the method is inapplicable.

Lunge gives the following table of densities of mixtures of para- and ortho-toluidine, water at 15° being taken as unity:—

Specific gravity at 15° C.	Ortho-toluidine. Per cent.	Specific gravity at 15° C.	Ortho-toluidine. Per cent.	Specific gravity at 20° C.	Ortho-toluidine. Per cent.	Specific gravity at 20° C.	Ortho-toluidine. Per cent.
1·0037	100	1·0016	82½	0·9995	65½	0·9989	50
36	99	15	82	94	65	38	49½
35	98	14	81	93	64	37	48½
34	97	13	80	92	63½	36	48
33	96	12	79½	91	62	35	47½
32	95	11	78½	90	61½	34	46½
31	94	10	77½	89	61	33	46
30	93½	09	77	88	60	32	45
29	92½	08	76	87	59	31	44½
28	91½	07	75	86	58½	30	44
27	91	06	74	85	58	29	43
26	90	05	73	84	57½	28	42
25	89½	04	72½	83	56½	27	41
24	88½	03	72	82	56	0·9926	40
23	88	02	71	81	55		
22	87	01	70	80	54½		
21	86½	1·0000	69	79	54		
20	86	0·9999	68½	78	53		
19	85	98	68	77	52½		
18	84½	97	67	76	51½		
1·0017	83½	0·9996	66½	0·9975	51		

A method of separating orthotoluidine from paratoluidine has been based by P. Schoop (*Chem. Zeit.*, ix. 1785; *Jour. Soc. Chem. Ind.*, v. 178) on the observation of Weith and Merz, that the acetyl-derivative of orthotoluidine is far less soluble in water than that of the isomer and of aniline. Schoop's method has been found unsatisfactory by several chemists, and need not be further described.

A method of estimating paratoluidine in admixture with ortho-

toluidine has been based by G. A. Schoen (*Chem. Zeit.*, xii. 494; *Jour. Soc. Chem. Ind.*, vii. 594) on the intensity of the red colour produced with potassium bichromate. If the specific gravity indicates the presence of more than 8 per cent. of paratoluidine it is reduced below that proportion by adding orthotoluidine. 1 c.c. of the oil is then dissolved in 2 c.c. of hydrochloric acid and 30 of water, and 1 c.c. of a cold saturated solution of bichromate of potassium added. The mixture is allowed to stand for an hour, with occasional stirring, and is then filtered. Orthotoluidine gives a black lake and a colourless liquid, but in presence of paratoluidine the precipitate is light brown, and the filtrate has a red colour, intense in proportion to the paratoluidine present. Pure aniline behaves like orthotoluidine, but in presence of the latter a red filtrate is produced. Hence aniline must be absent, or its amount must be deduced from the boiling-point and specific gravity of the sample, and a corresponding amount added to the standard mixture with which the sample is compared.

XYLIDINES. Amido-dimethylbenzenes. $C_6H_3(CH)_2.NH_2$.

Six isomeric bodies of the above formula are theoretically possible, and all of them are known. Thus :[1]—

Base.	Positions of Groups. $CH_3:CH_3:NH_2$	Boiling-Point, ° C.	Acetyl-Derivative.		Characters of Hydrochloride.
			Melting-Point, ° C.	Appearance, &c.	
v-Orthoxylidine,	1:2:3	223	134	White needles.	Moderately soluble white needles, containing 1 aq.
a-Orthoxylidine,	1:2:4	226 (melts at 49)	99	Long vitreous prisms.	Long, very thin prisms, containing 1 aq.
v-Metaxylidine,	1:3:2	214	176·8	White needles; not saponified by boiling alkali or acid.	Thin anhydrous plates; readily soluble.
a-Metaxylidine,	1:3:4	212	129	White needles.	Anhydrous rhombic tablets; slightly soluble in cold water.
s-Metaxylidine,	1:3:5	220	140·5	Large flat needles.	Large anhydrous needles.
Paraxylidine,	1:4:2	212·5	139	Long lustrous needles.	Flat needles or large tablets.

[1] The table is chiefly drawn up from the descriptions of the isomeric xylidines given by Roscoe and Schorlemmer (iii. part iv. page 406). The

The modifications of xylidine produced by nitrofying the xylenes of coal-tar naphtha and reducing the nitro-derivatives are chiefly *a*-orthoxylidine, *a*-metaxylidine, and paraxylidine, but two of the other isomers are also said to be produced. Only the *a*-meta-modification is of any value for the manufacture of azo-colouring matters, and of the cumidines, $C_6H_2(CH_3)_3.NH_2$, which are prepared by heating xylidine hydrochlorides with wood spirit. On this account, the useless isomers are removed as far as possible from the metaxylene before nitrofying (Vol. II. page 482), and in fact the presence of even a few units per cent. of orthoxylene will occasion considerable practical inconvenience by the formation of tarry matters during its conversion into xylidine. On the other hand, commercial xylidine often contains as much as 25 per cent. of paraxylidine. *v*-metaxylidine (1 : 3 : 2) is prepared by converting commercial xylidine into the sulphate, which is allowed to crystallise, and the base liberated from the mother-liquor by alkali. The fraction distilling between 212° and 216° is heated with acetic anhydride. The *v*-meta-acetxylidide formed is not acted on by boiling for several hours with four times its weight of dilute sulphuric acid containing 25 per cent. of H_2SO_4, but its isomers are decomposed. On cooling, the unchanged acetyl-compound separates, and after recrystallisation from hot water melts at

characters differ considerably from those attributed to the isomers by Wroblewsky (*Annalen*, ccvii. 91). Nölting and Pick (*Berichte*, xxi. 3150), however, consider that Wroblewsky's *v*-orthoxylidine was simply impure *v*-metaxylidine, and give the following table of characters of xylidine salts:—

	v-Orthoxylidine.	*as*-Orthoxylidine.	*v*-Metaxylidine.	Wroblewsky's so-called Orthoxylidine.
HYDROCHLORIDE, .	+ 1 H_2O	+ 1 H_2O	+½ H_2O; needles	+ ½ H_2O
Solubility in 100 of water at 18° C.,	11·2	Very soluble.	9·2	Very soluble.
NITRATE, . . .	Anhydrous.	Anhydrous.	Anhydrous.	Anhydrous.
Solubility in 100 of water at 18° C.,	6·6	0·4	2·2	2·7
NORMAL SULPHATE,	Anhydrous.	Anhydrous.	Anhydrous.	Anhydrous.
Solubility in 100 of water at 18° C.,	1·4	5·6	Very soluble.	...
ACID SULPHATE, .	Is not formed under ordinary conditions.		+ 2½ H_2O	+ 2½ H_2O
Solubility in 100 of water at 18° C.,	...	...	6·2	Very soluble.

176°·8 C. On heating it for some time to 200° C., with three parts of sulphuric acid containing 70 per cent. of H_2SO_4, the sulphate of *v*-metaxylidine is formed. This salt differs from the sulphate of the isomeric xylidines in its very ready solubility in water.

a-Orthoxylidine (1 : 2 : 4) is the only modification of xylidine which is solid at ordinary temperatures. By gradually evaporating its solution in petroleum ether, it is obtained in thick monoclinic prisms, but when rapidly deposited, or caused to solidify quickly, it forms transparent vitreous tablets. It melts at 49°, and is sparingly soluble in cold water, but readily in hot water, and also in alcohol and ether. Its aqueous solutions are not coloured by bleaching powder solution. The hydrochloride is readily soluble in water, but only slightly in strong hydrochloric acid; its aqueous solution imparts an intense yellow colour to fir-wood.

a-Metaxylidine (1 : 3 : 4), or ordinary xylidine, is best obtained by converting commercial xylidine into the hydrochloride and crystallising the product from water. Both the hydrobromide and hydrochloride are only slightly soluble in cold water. The last traces of impurity can be removed from metaxylidine by converting it into the acetyl-derivative, and recrystallising this body from benzene till it has a melting-point of 129°. It is then decomposed by sulphuric acid.

Paraxylidine (1 : 4 : 2) has a specific gravity of 0·980. It is prepared by treating commercial xylidine with fuming sulphuric acid containing sufficient sulphuric anhydride to convert the bases into sulphonic acids. The mixture is heated to 100° for some time, allowed to cool, and the solid mass pressed under water to separate metaxylidine-sulphonic acid in the crystalline state; or the hot liquid is poured upon ice, when the metasulphonic acid, being with difficulty soluble in dilute sulphuric acid, crystallises out. The mother-liquor is neutralised with chalk, filtered, precipitated with sodium carbonate, and again filtered. On concentrating the filtrate, the sodium salt of paraxylidine-sulphonic acid separates in nacreous plates, which are washed with a little cold water to free them from traces of the readily soluble meta-sulphonate. The salt yields paraxylidine on dry distillation with ammonium chloride, while the sodium salt of metaxylidine-sulphonic acid chars under the same treatment. Paraxylidine may also be obtained by nitrofying and reducing paraxylene, which may readily be prepared from commercial xylene (Vol. II. page 483).

CUMIDINES. Amido-trimethylbenzenes. $C_6H_2(CH_3)_3.NH_2$. Various isomerides of this formula are known. The solid variety of commercial cumidine is made by heating xylidine hydrochloride and methyl alcohol together under pressure, to about 300°.

The bases are liberated and converted into nitrates, and the difficultly soluble nitrate of pseudocumidine separated from the mother-liquor. The base is again liberated and distilled. The fraction passing over between 230° and 240° crystallises on cooling, and consists of amido-pseudocumene:—

$$(CH_3 : CH_3 : CH_3 : NH_2 = 1 : 2 : 4 : 5).$$

It crystallises from hot water in long needles, and from alcohol in large prisms, melts at 68°, and boils at 234°–236°. When converted into diazocumene it can be used for the preparation of azo-colours by reaction with naphthol-mono- and di-sulphonic acids.

ISODURIDINE. Amido-tetramethylbenzene. $C_6H(CH_3)_4.NH_2$.

When the hydrochloride of pseudocumidine is heated with methyl alcohol to 300°, the hydrochloride of isoduridine is formed. The free base, which also occurs among the bye-products of the manufacture of pseudocumidine, is an oily liquid which boils at 250°–253°, and solidifies on cooling to crystals which melt at 14°.

AMIDO-PENTAMETHYLBENZENE. $C_6(CH_3)_5.NH_2$.

This base is obtained by heating dimethyl-α-pseudocumidine with methyl iodide. It forms large white needles, melting at 151° and boiling at 277°.

Aniline Oils.

The term "aniline oils" is applied commercially to all the different varieties of aniline manufactured on a large scale, equally whether the product in question consists of nearly pure aniline, of toluidine, or of a mixture of the two. The method of manufacturing the different varieties of aniline oil is substantially the same, the composition of the product depending on that of the hydrocarbon employed. The details of the method of manufacture are, of course, subject to variation, but the following is an outline of the method pursued in a well-known aniline works:— Crude coal-tar naphtha is redistilled to a temperature of 170° C. The *product of the distillation, called "once-run naphtha," is* treated with strong sulphuric acid (sp. gr. 1·845) which removes the bases, hydrocarbons of the ethylene and crotonylene series, and some of the higher homologues of benzene. A subsequent treatment with milk of lime or caustic soda eliminates the phenols and other bodies of an acid character. The purified oil is washed with water and redistilled to obtain "50/90 benzol," and this when fractionated with the acid of a dephlegmating column at once yields 99 per cent. benzol, toluol, and solvent naphtha (compare Vol. II. page 487). Solvent naphtha is now generally further treated for the isolation of xylene, but the benzols and toluol are directly converted into the nitro-compounds by placing them

in a vessel surrounded with cold water, and gradually running in a cold, previously made mixture, of 150 per cent. by weight of nitric acid of 1·4 specific gravity with 200 per cent. of concentrated sulphuric acid. When the reaction is complete the mixture is allowed to stand, and the lower layer of acid is tapped off and concentrated again in glass for repeated use. The nitrobenzol is washed several times with caustic soda, and then treated with open steam to drive off unchanged benzol and "light stuff." The nitrobenzol (or nitrotoluol obtained in a precisely similar manner) is then placed in a still with hydrochloric acid, and borings or filings of grey cast iron added gradually. High-pressure steam is blown in, and the nitrobenzol which distils over is separated from the condensed water, and returned to the still until the complete solubility of the distilled oil in hydrochloric acid shows that the reaction is complete. Milk of lime is then introduced, and the liberated aniline distilled off by the aid of steam. Aniline sinks to the bottom of the condensed water, but when toluidine is being made the oil floats on the surface. The condensed water contains from 2 to 3 per cent. of dissolved bases, and is converted into steam for the aniline stills. The iron is converted into a black paste, consisting chiefly of Fe_3O_4, which is sold for purifying gas. The aniline oil is distilled to separate water, &c. The addition of lime to liberate the aniline is not strictly necessary, and in many works it is omitted. The first reaction seems to be :—

$$C_6H_5.NO_2 + Fe_3 + 6HCl = 3FeCl_2 + C_6H_5.NH_2 + 2H_2O.$$

The ferrous chloride formed also acts as a reducing agent, being converted into ferric chloride, which in presence of water gives ferric oxide and aniline hydrochloride. The end-products are chiefly aniline, ferroso-ferric oxide, and a weak solution of ferrous chloride. The hydrochloric acid seems to act chiefly as a carrier, so that the general reaction may be represented by the equation :— $4C_6H_5.NO_2 + 9Fe + 4H_2O = 3Fe_3O_4 + 4C_6H_5.NH_2$. Acetic acid was formerly employed in place of hydrochloric acid, but its use is now almost, if not entirely, obsolete. Its use in too large a proportion tended to the formation of acetanilide. Too large an excess of iron, or its too rapid addition, may cause loss from a reproduction of benzene, while deficiency of both iron and acid favours the production of azo-benzene.

Composition and Assay of Aniline Oils.

There are three leading kinds of aniline oil now recognised in the market, namely :—(1) Pure aniline oil; (2) aniline oil for red; and (3) toluidine. The demand for xylidine for the manufacture of azo-reds has considerably influenced the character

of commercial aniline; since the 50/90 benzol, which was commonly used for the manufacture of "aniline for red," formerly contained a notable quantity of xylene, which is now removed and converted separately. Since the employment of dephlegmating columns has become usual, benzene and toluene of almost constant boiling-points have been manufactured. From the pure hydrocarbons the corresponding bases are prepared, while from the intermediate oil, containing about 25 per cent. of benzene and 75 of toluene, an aniline oil for red is manufactured, which contains about 25 per cent. of aniline, from 20 to 25 of paratoluidine, and 45 to 50 per cent. of orthotoluidine.[1]

In addition to the foregoing leading qualities of aniline oil, products of very varying composition and degrees of purity have to be dealt with by the dye-manufacturer. Thus in making magenta by the arsenic acid process, fully one-fourth of the aniline distils off and is condensed. But this recovered aniline is found on rectification to have a considerably higher density than the original oil (1·015 to 1·009 against 1·0075), and to consist almost entirely of aniline and orthotoluidine, whereas the original oil contained from 15 to 25 per cent. of paratoluidine. This is either employed for the manufacture of safranine or very red shades of blue, or crude paratoluidine is added to it in such proportion as to bring it approximately to the original composition. Similarly, in the manufacture of magenta by the nitrobenzene process, the recovered aniline contains notable quantities of nitrobenzene, while from other processes methylated and ethylated anilines are obtained. *Recovered anilines* are deeper in colour and of greater body than unused oils, and often have a strong and somewhat characteristic odour. They are rarely met with outside the colour-works in which they have their origin.

On next page is a tabulated list of the more important or frequently-occurring constituents of aniline oils.[2] With the exception of aniline and its homologues, and the substituted anilines, very little is known respecting the effect of the bodies formulated in the table on the colouring matters produced. For the most part the objectionable impurities are got rid by fractionating the crude aniline oil.

[1] The composition of aniline oil for red is often judged of by the consumer solely from the specific gravity, and he or the aniline-maker adjusts it accordingly by adding aniline or toluidine to the crude oil as the gravity may indicate.

[2] Hell and Rockenbach (*Ber.*, xxii. 505) have investigated some other non-basic constituents of aniline and toluidine tailings.

Name.	Formula.	Melting-Point °C.	Boiling-Point °C.	Remarks.
Aniline, . . .	$C_6H_5.NH_2$	− 8	183·7	See page 43.
Toluidine, ortho-; 1 : 2	$C_6H_4(CH_3).NH_2$	below − 20	199	See page 52.
Toluidine, meta-; 1 : 3	$C_6H_4(CH_3).NH_2$	below − 13	197	See page 52.
Toluidine, para-; 1 : 4	$C_6H_4(CH_3).NH_2$	45	198	See page 52.
Xylidine (several isomers), . .	$C_6H_3(CH_3)_2.NH_2$	...	212–226	See page 57.
Cumidine (several isomers, chiefly Pseudocumidine),	$C_6H_2(CH_3)_3.NH_2$	63	235	See page 60.
Methyl-aniline, .	$C_6H_5.NH(CH_3)$	...	192	See page 73.
Dimethyl-aniline, .	$C_6H_5.N(CH_3)_2$	0·5	192	See page 74.
Ethyl-aniline, . .	$C_6H_5.NH(C_2H_5)$	...	204	See page 73.
Diphenylamine, .	$C_6H_5.NH(C_6H_5)$	54	302	See page 79.
Acetanilide, . .	$C_6H_5.NH(C_2H_3O)$	112	295	See page 68.
Acetotoluide, ortho-	$C_6H_4(CH_3).NH(C_2H_3O)$	65–66	302–304	Produced by action of heat on toluidine acetate.
Acetotoluide, para-	$C_6H_4(CH_3).NH(C_2H_3O)$	147	300–307	Produced by action of heat on toluidine acetate.
Nitranilines, . .	$C_6H_4(NO_2).NH_2$.	...	...	From imperfect reduction of dinitrobenzene.
Paraniline, . .	$C_{12}H_{14}N_2$	192	330	...
Xenylamine, . .	$C_{12}H_9.NH_2$	45	322	...
Phenylene-diamine (para-), . . .	$C_6H_4:(NH_2)_2$	63	287	Reduction of dinitrobenzene (page 87).
Toluylene-diamine (para-), . . .	$C_6H_3(CH_3):(NH_2)_2$	99	283–285	See page 88.
Azobenzene, . .	$C_6H_5.N_2.C_6H_5$	65	298	Imperfect reduction of nitrobenzene.
Nitrobenzene, . .	$C_6H_5.(NO_2)$	3	210	Vol. II. page 476.
Dinitrobenzenes, ortho-	$C_6H_4(NO_2)_2$	118	...	Monoclinic tables.
Dinitrobenzenes, meta-	$C_6H_4(NO_2)_2$	90	...	Long needles or thin rhombic tables.
Dinitrobenzenes, para-	$C_6H_4(NO_2)_2$	172	...	Monoclinic needles.
Nitrotoluenes, ortho-	$C_6H_4(CH_3)(NO_2)$	below − 20	223	Sp. gr. 1·163 at 23°·5.
Nitrotoluenes, meta-	$C_6H_4(CH_3)(NO_2)$	16	230	Sp. gr. 1·168 at 22°.
Nitrotoluenes, para-	$C_6H_4(CH_3)(NO_2)$	54	238	...
Benzene, . . .	C_6H_6	5·5	80·5	Vol. II. page 469.
Toluene, . . .	$C_6H_5(CH_3)$	below − 20	111	Vol. II. page 479.
Amidothiophene, .	$C_4H_3S.NH_2$	...	...	...
Paraffins, . . .	C_2H_{2n+2}	...	...	Especially in aniline oils derived from cannel-tar benzols.

The *assay* of aniline oils is usually limited to observations of the colour, odour, and specific gravity, supplemented by a careful fractional distillation and tests for water, nitrobenzene, hydrocarbons, &c.

The specific gravity of aniline oil is a valuable indication of its composition. The observation must be made by the plummet or specific-gravity bottle at exactly 15° C., and the result referred to water at the same temperature taken as unity.[1]

[1] P. Schoop (*Chem. Zeit.*, ix. 178; *Jour. Soc. Chem. Ind.*, v. 178) gives the density of pure aniline as 1·0377 at 1° C.; orthotoluidine as 1·0143; and paratoluidine as 1·0045 at the same temperature; the coefficient of expansion being in each case 0·00081 for 1° C.

The following figures represent the densities as thus observed:—

	Specific gravity at 15° C.
Pure aniline, ...	1·0268.
Aniline oil for red, . . .	1·0075 to 1·0012.
Orthotoluidine, ...	1·0037.
Mixture of equal parts of ortho- and para-toluidine, . .	·9975.
Paratoluidine, ...	Solid.

The odour of pure aniline is very different from that of the toluidines. The presence of toluidine in aniline is indicated by the density of the sample, its diminished solubility in dilute alcohol (page 65), and by the results of the fractional distillation (page 65). In addition to these characters, the following tests are sometimes of service:—

Pure aniline affords no rosaniline on treatment with oxidising agents, but if toluidine be present magenta is readily formed. The test is best made by mixing 5 c.c. of the sample of aniline with an equal measure of a concentrated solution of arsenic acid, containing about 75 per cent. of As_2O_5 and having a density of 2·04. The mixture, contained in a small flask or long test-tube, is immersed in a paraffin-bath heated to 180° C. The mixture rapidly changes in colour, and swells considerably. When the action is complete, the contents of the tube acquire a metallic bronze appearance and no longer intumesce. The product is treated with boiling water, when, if the sample contained toluidine, arseniate of rosaniline dissolves and communicates an intense crimson colour to the liquid. Neither pure aniline nor toluidine alone gives this reaction.

If a sample of commercial aniline be mixed with some solid magenta and a few drops of glacial acetic acid, and the whole heated to 180° C., as described above, ammonia is abundantly evolved, and in a short time the mixture becomes intensely blue from the formation of t r i p h e n y l - r o s a n i l i n e. With pure aniline the blue is very pure in shade, but when toluidine or xylidine is treated in a similar manner the product is intensely purple, and a mixture of the bases gives proportionate intermediate shades of colour. If a little of the "melt" be withdrawn from the tube, diluted considerably with alcohol, a few drops of acetic acid added, and then streaked on white filter-paper by means of a glass rod, the purple tint is readily observed, especially if the paper be held up before a gas-flame.

A valuable indication of the general composition of an aniline oil is obtained by submitting the sample to fractional distillation, and noting the proportions of distillate obtained at various tem-

peratures. The distillate may be measured after each rise of 5 degrees in the boiling-point of the sample, or the temperature may be observed when each consecutive 5 or 10 per cent. fraction has passed over. The latter is the plan now commonly adopted, 100 c.c. of the sample being employed, and the arrangement of the apparatus being exactly the same as in the fractional distillation of benzols (Vol. II. page 495).

The heat is applied cautiously at first, in order to dissipate any water. When this is effected, which will be known by the rapid rise of the thermometer, the heat is so regulated that the distillate shall fall in distinct drops, about sixty per minute. With each increase of 10 c.c. in the volume of the distillate the temperature indicated by the thermometer is observed and recorded, the process being continued till 90 or 95 c.c. have passed over.

A very simple test for aniline oils was devised and communicated to the writer by the late B. Nickels, who found it to give useful results, and to indicate differences between samples not readily distinguishable by the ordinary fractional distillation process. The test is based on the greater solubility in dilute alcohol of aniline as compared with toluidine and xylidine, and is thus performed:—5 c.c. measure of the sample is taken with a pipette and diluted to 40 c.c. with methylated spirit. Distilled water is then gradually added from a burette, with constant shaking, till a permanent turbidity is produced, when the volume of water employed is noted. Operating in this way, a sample of very pure aniline required 126 c.c. of water to produce permanent turbidity. The following figures, obtained by B. Nickels in 1881, show the results yielded by three typical specimens of commercial aniline as then manufactured:—

	A. Pure Aniline.	B. Heavy Aniline.	C. Toluidine.
Colour,	Pale amber.	Amber.	Deep brown.
Specific gravity at 15°·5 C.,	1·025	1·011	1·002
Water required for precipitation,	106·4 c.c.	78·7 c.c.	63·2 c.c.
	° C.	° C.	° C.
10 per cent. distilled over at	183¼	189	195
20 „ „ „	183½	189¾	195¾
30 „ „ „	183¾	190	196
40 „ „ „	184	191	196½
50 „ „ „	184¼	191½	197
60 „ „ „	184	192¼	197½
70 „ „ „	184	193	198
80 „ „ „	184	194½	198½
90 „ „ „	184½	197	199¾
95 „ „ „	184¾	201	

Sample A was a fair commercial specimen of the quality known as "pure aniline," and actually contained some 95 per cent.

of real aniline. An article of this high purity is required for the manufacture of aniline blue, triphenyl-rosaniline (see page 64), any notable admixture of toluidine resulting in a product dyeing with reddish tinge.[1]

The quality known as "heavy aniline," exemplified by B, is a fair sample of aniline oil for red (see page 62). This class of aniline is produced from benzols containing a considerable proportion of toluene, and the aniline oil itself is a mixture of aniline and toluidines. Good samples of aniline oil for red contain from 35 to 42 per cent. of real aniline, 35 to 50 per cent. of orthotoluidine, and 14 to 24 per cent. of paratoluidine.

R. J. Friswell thinks 100 c.c. an undesirably small quantity for fractional distillation. He prefers to operate on 250 c.c., which he distils in a flask with a side-tubulure, and he recommends an observation of the temperature at which the last drop disappears from the bottom of the flask. A naked flame is used, and a few fragments of platinum wire or fire-brick added to the contents of the flask. The following figures were obtained by Friswell (Thorpe's *Dict. Applied Chem.*, i. 165) by the examination of commercially pure aniline.

	No. 1.	No. 2.	No. 3.
Specific gravity at 15° C., ...	1·02710	1·02684	1·02690
	° C.	° C.	° C.
10 per cent. over at, ...	184·7	184·6	184·6
20 " "	184·7	184·8	184·6
30 " "	184·7	184·8	184·7
40 " "	184·7	184·8	184·7
50 " "	184·8	184·8	184·8
60 " "	184·9	184·8	184·8
70 " "	185·0	184·8	184·9
80 " "	185·1	184·8	184·9
90 " "	185·1	184·8	185·0
Dry at, ...	186·7	186·8	...

Any *water* present in aniline oil will be found in the very first portions (first fraction of 10 per cent.) whenever the sample is submitted to distillation. It takes the form of globules, which are not miscible with the next fraction of the distillate nor with petroleum spirit. Water may exist in aniline in any proportion from a trace up to 3 or 4 per cent., but a good commercial rectified specimen should not contain more than 0·5 per cent. Aniline is readily soluble in a strong aqueous solution of aniline hydro-

[1] In good samples the boiling-points hold closely together, differing by one or two degrees only. Inequalities or jumps in the boiling-point, especially at the beginning and end of the distillation, indicate badly-made samples or mixtures.

chloride. A solution of the kind, of 1·08 specific gravity, is stated by Watson Smith to be sometimes sold as aniline oil, which in colour and taste it closely resembles. Such a fraud would be at once detected on distillation.

Benzene, *toluene*, and other *hydrocarbons* will separate when the first fraction of 10 per cent. (10 c.c.) is treated with an equal volume or slight excess of hydrochloric acid, and water added to 100 or 150 c.c. They assume the form of oily globules which float even on diluting the liquid. The best samples of pure aniline show only a slight opalescence when thus treated, but the smell of the "light stuff" (Vol. II. page 488) is always perceptible. In recovered anilines these impurities exist to a notable extent, since they survive the reactions by which the bases are consumed. Aniline for red usually contains somewhat more hydrocarbons than pure aniline.

Nitrobenzene and *nitrotoluene* may be recognised, even when mere traces are present, by the milky appearance of the liquid produced by saturating 10 c.c. of the original sample of oil with hydrochloric acid. On diluting the liquid with water, and leaving it at rest for some hours, any considerable quantity of nitrobenzene will collect at the bottom in the form of oily globules, which, after separating the acid liquid, may be identified by the smell and other characters. Still smaller quantities of nitrobenzene may be recognised if the "tailings" be operated upon, instead of the original sample. Nitrobenzene occurs more frequently in magenta-aniline and toluidine than in the oils of lower boiling-point.

Nitrobenzene is also indicated by the yellow colour of the froth produced when the sample is violently agitated.

Acetanilide and *acetotoluide* were impurities characteristic of aniline prepared by the reduction of nitrobenzene with acetic acid and iron, but are now rarely met with in aniline oils. In any case they would become concentrated in the "tailings," together with phenylene-diamine, azobenzene, paraniline, "xenylamine," &c.

Aniline tailings is the name applied to the least volatile portion of aniline oils. They contain little or no aniline; some toluidine, xylidine and cumidine; nitrobenzene and its homologues; and some or all of the bye-products tabulated on page 63 which boil above 200° C.

The composition and special methods of examination of commercial *toluidine* are described on page 54 *et seq.*

Anilides.

The anilides are derivatives of aniline in which one or both of the hydrogen-atoms of the amido-group are replaced by acid-

radicals. The homologues of aniline yield similar derivatives (*e.g.*, aceto-toluide, page 52). The most important and typical member of the class is acetanilide or phenylacetamide:—

$$C_6H_5.NH(C_2H_3O)\ ;\ \text{or}\ C_2H_3O.NH(C_6H_5)\ .$$

A number of derivatives of acetanilide have been prepared, and certain of them have found some employment as analgesics and antipyretics, as for instance:—

Acetanilide. Phenylacetamide. Antifebrin. $C_6H_5.NH(C_2H_3O)$.
Bromacetanilide. Antiseptin. Brominated antifebrin. (Page 71.) $C_6HBr.N_4H(C_2H_3O)$.
Methylacetanilide. Exalgin. Methylated antifebrin. (Page 71.) $C_6H_5.N(CH_3)(C_2H_3O)$.
Aceto-amidophenol. Hydroxy-antifebrin. $C_6H_4(OH).NH(C_2H_3O)$.
Aceto-anisidine. Methacetin. Methoxy-antifebrin. (Page 85.) $C_6H_4(O.CH_3).NH(C_2H_3O)$.
Acet-phenethidine. Phenacetin. *Ethoxy-antifebrin.* (Page 81.) $C_6H_4(O.C_2H_5).NH(C_2H_3O)$.
Amido-phenacetin. Phenocoll. $C_6H_4(O.C_2H_5).NH(C_2H_2O.NH_2)$.

Most of these bodies are described in the following pages. The relationship of antifebrin to hypnone, hydracetin (pyrodine), and phenyl-urethane, is shown by the following formulæ:—

Acetophenone. Hypnone (Part I. page 23). $C_6H_5.(CO.CH_3)$.
Acetanilide. Antifebrin (see below). $C_6H_5.NH.(CO.CH_3)$.
Acet-phenylhydrazine. Hydracetin. (Page 28.) $C_6H_5.NH.NH.(CO.CH_3)$.
Lævulinyl-phenylhydrazine. Antithermin. (Page 31.) $C_6H_5.NH.NH.(C_5H_7O_2)$.
Phenyl-urethane. Euphorin. (Page 72.) $C_6H_5.NH.(CO.O.C_2H_5)$.

ACETANILIDE. PHENYLACETAMIDE. $C_6H_5.NH(C_2H_3O)$.

This substance was originally obtained by the action of acetyl chloride on aniline. It is more conveniently prepared by boiling aniline with glacial acetic acid for many hours under an inverted condenser, until the product solidifies on cooling. The mass is then melted and poured into water, to remove unconverted aniline and acetic acid. It may be purified by distillation and crystallisation from alcohol, benzene, or hot water, from which it separates in colourless unctuous laminæ, resembling boric acid, soluble in about 190 parts of cold or 18 of boiling water. Acetanilide is odourless, but produces a slight burning sensation on the tongue. It occurs commercially as a crystalline powder or scales. It melts at 112°–113°, and distils unchanged at 295° C. Acetanilide

dissolves in $3\frac{1}{2}$ parts of alcohol, and is very soluble in ether, chloroform, and benzene, yielding neutral solutions.

Acetanilide is a weak base. The *hydrochloride* is obtained by passing hydrochloric acid gas through a solution of acetanilide in acetone. It forms needles which are decomposed into their constituents by water, and gradually converted into acetic acid and aniline hydrochloride on exposure to moist air.

Acetanilide dissolves in strong sulphuric acid without change of colour. On treating the solution with nitric acid, the acetanilide is converted chiefly into *para*-nitroacetanilide (page 50), some of the *ortho*-compound and, in presence of a large excess of sulphuric acid, a little of the *meta*-compound being also formed. Nitrous acid, passed into its acetic acid solution, converts acetanilide into an unstable nitrosamine, $C_6H_5.N(C_2H_3O)(NO)$. When heated with zinc chloride to about 250°, acetanilide yields *flavaniline*, $C_{16}H_{14}N_2,HCl$ (Part I. page 245). Treated in alcoholic solution with sodium ethylate, acetanilide yields a sodium derivative, $C_6H_5.NNaC_2H_3O$, but when this is boiled with water it splits into aniline and sodium acetate. Acetanilide behaves like aniline on treatment with caustic alkali and chloroform (page 46), and the formation of the disagreeably smelling isonitrile is a delicate reaction for its presence (compare page 83).

Acetanilide behaves like aniline when treated with phenol and solution of bleaching powder (page 45).

When treated with a solution of potassium chlorate in strong sulphuric acid, acetanilide gives a red coloration, changed to yellow on dilution. With a crystal of a nitrite and a drop of concentrated hydrochloric acid it produces a yellow colour, changing on heating to green and blue; and, on evaporating the liquid to dryness, an orange residue is obtained, changed to red on adding ammonia (Vitali).

When acetanilide is heated gently with mercurous nitrate, a body is produced which dissolves in alcohol with green colour (Yvon). If a few centigrammes of acetanilide be gently heated with two or three drops of a solution of mercurous nitrate, and when solution has been effected two or three drops of sulphuric acid added, a blood-red coloration will be produced (Cella and Arzeno). The same reaction is produced by phenol, resorcinol, thymol, and salicylic, gallic, and tannic acids, but not by benzoic acid.

Acetanilide gives no colour-reactions with ferric chloride, nitrites in very dilute solutions, or potassium bichromate in aqueous solution. These reactions distinguish it from antipyrine and kairine.

Various other colour-reactions of acetanilide have been described.

As a rule, the most satisfactory method for its positive identification is to heat the substance with alcoholic potash, dilute with water, and shake with ether. The ethereal layer is examined for aniline, while the aqueous liquid is tested for an acetate.

To detect acetanilide in urine, Vulpius boils the liquid with hydrochloric acid, cools, extracts with ether, and tests the ethereal solution with phenol and bleaching powder solution.

E. Ritsert (*Pharm. Zeit.*, xxxv. 306; *Jour. Chem. Soc.*, lviii. 1349) gives the following tests for the purity of commercial acetanilide:—The sample should leave no ash on ignition, and after drying for two hours at 105°, should melt at 114°. A higher or lower melting-point indicates the presence of aceto-toluides. 0·1 gramme dissolves in 1 c.c. of strong hydrochloric acid to a clear solution, which, after a few minutes, precipitates acetanilide hydrochloride (methyl-acetanilide does not yield a similar reaction). No change should be produced on adding a drop of nitric acid, which, after a time, produces a yellow or brown coloration if phenacetin or methacetin be present. If 0·1 gramme be boiled in portions in 2 c.c. of strong hydrochloric acid, the solution cooled, and a drop or two of chlorine water added, a fine blue coloration is produced. The aqueous solution of acetanilide should be free from acid reaction (indicating acetic acid). On boiling it and adding ferric chloride, a deep reddish-brown colour should be produced, destroyed by a mineral acid. If a drop of dilute solution of potassium permanganate (1 : 1000) be added to a boiling aqueous solution of 1 gramme of acetanilide in 30 c.c. of water, the pink coloration at first produced should persist at least five minutes, and should not change to yellow on again boiling. Precipitation at this stage indicates the presence of free aniline, resinous products, aceto-toluides, or other impurities.

In the *additions* (1890) to the *British Pharmacopœia*, acetanilide is described as melting at 235° F. (=112°·8 C.), and dissolving in sulphuric acid without coloration. The solution in 18 parts of boiling water should be clear, neutral, and odourless; and *after cooling* should not be coloured on adding ferric chloride. This is directly opposed to the experience of Ritsert above quoted. In the *German Pharmacopœia* the direction is to add ferric chloride to a cold saturated solution, thus avoiding the dissociation and formation of acetic acid liable to occur on boiling. According to the *German Pharmacopœia*, on heating with caustic alkali solution, acetanilide gives off an aromatic vapour, which, after addition of a drop of chloroform and renewed application of heat, is changed to the disagreeable smell of the isonitrile. Further, 0·1 gramme of acetanilide should yield a clear solution when boiled with 1 c.c. of

hydrochloric acid for one minute; and, after adding to the liquid 2 c.c. of carbolic acid, a cloudy red coloration should be produced by solution of bleaching powder, changed to a permanent indigo-blue (indophenol) on adding excess of ammonia.

Acetanilide has powerful antipyretic properties, and has received an extensive application in medicine under the name of "antifebrin,"[1] though dangerous symptoms are sometimes produced by it (*Pharm. Jour.*, [3], xx. 1059). The dose is from 3 to 10 grains.

According to Salzer, commercial antifebrin is liable to certain unchanged aniline, which may be detected by dissolving the sample in cold hydrochloric acid, and pouring on the liquid a solution of bleaching powder. Pure acetanilide yields a white precipitate, which dissolves on shaking the liquid, but after a time colourless silky needles separate. In presence of aniline the well-known violet coloration is produced.

Acetanilide has been used as an adulterant of antipyrine (page 36). The melting-points of the pure substances are nearly identical; but a mixture of equal proportions of the two melts at 45° C.

Of the three isomeric *aceto-toluides* (page 52), only the meta-compound possesses antipyretic properties.

Para-brom-acetanilide, $C_6H_4Br.NH(CO.CH_3)$, has been introduced as a remedy under the name of "antisepsin." It forms small pearly prisms, melting at 164°·5, and devoid of taste or smell. It is soluble with difficulty in cold, but readily in hot water, as also in alcohol and ether.

Acet-methylanilide or *Methyl-acetanilide*, $C_6H_5.N(CH_3)(C_2H_3O)$, is prepared by warming together methylaniline and acetyl chloride. The product is boiled with water, when the new body crystallises on cooling. Methylacetanilide has been introduced as an anti-rheumatic and analgesic under the name of "exalgin." In doses

[1] When administered to rabbits, acetanilide is oxidised to para-amidophenol, $C_6H_4(OH).NH_2$, with complete elimination of the acetyl-group. In dogs there is a small formation of para-amidophenol, but the chief change consists in a simultaneous oxidation of the aniline-residue to ortho-amidophenol, of the acetyl-group to carboxyl, and in the formation of carbonyl-ortho-hydroxyamidophenol, $C_6H_3(OH)\left\{\begin{matrix}NH\\O\end{matrix}\right\}CO$, the anhydride of which is excreted in the urine as a sulphate. In both the rabbit and the dog the amido-phenols are also eliminated as sulphates. In man, the acetyl-group is not wholly oxidised, the urine containing the sulphate of aceto-par-amidophenol. In all cases there is an oxidation of one of the hydrogen atoms of the benzene-nucleus to hydroxyl, while the proportion of ethereal sulphates is increased (compare "Aniline," page 46), the urine is red from excess of bilirubin, reduces alkaline cupric solution, and is strongly lævo-rotatory; the optically active body probably being the above-mentioned sulphate (Gressly and Nencki, *Monatsh.*, xi. 253).

of ½ to 4 grains its effects are said to be very satisfactory. Exalgin forms fine needles or large white tablets (compare "Acetanilide"). It melts at 100°–101°, boils without decomposition between 240° and 250°, and is slightly soluble in cold water, but more so in boiling, and very soluble in water containing a little alcohol. It is saponified with difficulty by caustic alkali, but completely by concentrated hydrochloric acid, with formation of acetic acid and methylaniline.

Hirschsohn states that exalgin may be distinguished from antifebrin and phenacetin by treating 1 gramme with 2 c.c. of chloroform, which dissolves the exalgin only. A chloroformic solution of exalgin remains clear on adding ten measures of petroleum ether, whereas the solutions of antifebrin and phenacetin become turbid. 20 per cent. of acetanilide, or 10 of phenacetin, may be detected in exalgin by these reactions. An aqueous solution of antifebrin gives a bromo-derivative on adding bromine-water, thus differing from exalgin and phenacetin.[1]

BENZANILIDE, $C_6H_5.NH(CO.C_6H_5)$, is obtained by the action of benzoyl chloride on aniline, or by boiling together equivalent quantities of benzoic acid and aniline. It forms a white, crystalline powder, melting at 160°–161° and volatile without decomposition. It is almost insoluble in water, but dissolves in fifty-eight parts of cold, or seven of boiling, alcohol, crystallising on cooling in nacreous plates. It is difficultly soluble in ether. Benzanilide is not attacked by aqueous alkalies or acids, but is saponified by fusion with caustic potash. It has been found valuable as an antipyretic for children, in doses of 2 to 8 grains, and is said not to produce objectionable secondary effects.

PHENYL-URETHANE. ETHYL CARBANILATE. $C_6H_5.NH(CO.OC_2H_5)$. This compound has recently acquired a practical interest owing to its introduction as a synthetic remedy under the name of "euphorin." It is produced by the reaction of aniline on ethyl-chlorocarbonate, and occurs as a white crystalline powder, of a faintly aromatic odour and scarcely perceptible taste, which subsequently becomes acrid and clove-like. It melts at 49° to 51°, boils at 237°, and is only slightly soluble in cold water, but very freely soluble in alcohol, and sufficiently soluble in sherry and other alcoholic liquids to be conveniently given in solution in such menstrua. According

[1] Exalgin may also be distinguished from antifebrin, methacetin, and phenacetin by treating 2 grains (or 0·1 gramme) with 20 minims (or 1 c.c.) of concentrated hydrochloric acid. Phenacetin remains insoluble. Antifebrin dissolves, but separates again in crystals of the hydrochloride. Methacetin also dissolves, but is recognised by the reddish-brown coloration produced on adding one drop of nitric acid.

to Sansoni, after administration of phenyl-urethane, the urine shows the para-amidophenol reaction either directly or after distillation with potassium carbonate. The proportion of urea is increased, but the urine is free from phenol, aniline, albumin, and sugar.

Substituted or Alkylated Anilines.

These bases result from the replacement of one or both of the hydrogen atoms of the amido-group of aniline by alkyl or other basylous radicals.

The bases of this class are obtained by heating the hydrochloride or other salt of aniline (or its homologues) with the alcohol with which it is intended to react, or the halogen salt of this alcohol with free aniline.

The only substituted anilines which require special description are the following:—

	Formula.	*Specific Gravity.*	*Boiling-Point.*	*Reference.*
Methyl-aniline, . . .	$C_6H_5.NH(CH_3)$	·976 at 15°	192	Page 73.
Dimethyl-aniline, . .	$C_6H_5.N(CH_3)_2$	·9553 at 15°	192	Page 74.
Ethyl-aniline, ...	$C_6H_5.NH(C_2H_5)$	·954 at 18°	204	...
Diethyl-aniline, . . .	$C_6H_5.N(C_2H_5)_2$	·937 at 13°	213·5	Page 79.
Phenyl-aniline (Diphenylamine), .	$C_6H_5.NH(C_6H_5)$	1·161	302	Page 79.
Diphenyl-aniline (Triphenylamine), .	$C_6H_5.N(C_6H_5)_2$	...	...	Page 80.

Diphenylamine is a very weak base, and in triphenylamine the basic character is entirely lost.

METHYL-ANILINE. $C_6H_5.NH(CH_3)$.

This base is obtained by the action of iodide, nitrate, or chloride of methyl on aniline, or by heating methyl alcohol with aniline hydrochloride.[1] In all cases dimethyl-aniline is formed simultaneously, and hence in the production of mono-methylaniline a portion of the aniline remains, in practice, unattacked.[2]

[1] Pure methylaniline may be obtained by the reaction of methyl iodide on sodium acetanilide, $C_6H_5.NNa(C_2H_3O)$, and saponification of the resultant compound by caustic alkali.

[2] To separate this from its mono- and di-methyl-derivatives, dilute sulphuric acid is added as long as aniline sulphate continues to separate. The sulphuric acid solution is separated from the solid aniline sulphate by pressure in a linen cloth, and the expressed liquid treated with caustic soda. The substance which separates is dried and treated with acetyl chloride until no further rise of temperature is observed, when the product is poured into cold water. On cooling, methyl-acetanilide, $C_6H_5.N(CH_3)(C_2H_3O)$, separates in long needles, while dimethylaniline hydrochloride remains in solution.

Methylaniline is a liquid boiling at 192°. It resembles aniline, but is lighter than water, and its odour is stronger and more aromatic. The *sulphate* is soluble in ether and uncrystallisable. A solution of bleaching powder first colours it violet and then brown. The conversion of methylaniline into toluidine is referred to on page 41.

Methylaniline-nitrosamine, $C_6H_5.N(CH_3)(NO)$, separates as a yellow oil on treating a cold solution of methylaniline hydrochloride with sodium nitrite, while any aniline and dimethylaniline are converted into soluble products. If the nitrosamine be extracted by ether, and treated with tin and hydrochloric acid, it is reduced to methylaniline, which may thus be obtained in a pure state (compare page 7). The nitrosamine is destitute of basic properties. It has an aromatic odour, and may be distilled in a current of steam, but not alone. When methylaniline-nitrosamine is warmed with phenol and sulphuric acid, the mixture diluted with water and saturated with caustic alkali, it yields the intense green-blue coloration produced by all nitrosamines (Liebermann's reaction). When heated with alcoholic hydrochloric acid it undergoes molecular transformation into paranitroso-methylaniline, $C_6H_4(NO).NH(CH_3)$, a body crystallises in green-plates or steel-blue prisms, and otherwise resembling paranitroso-dimethylaniline (page 75).

DIMETHYL-ANILINE. $C_6H_5.N(CH_3)_2$.

This important base is obtained by the action of excess of methyl iodide on aniline. On the large scale, methyl iodide was formerly employed, but was afterwards replaced by the nitrate, and this again (owing to its explosive properties) was superseded by the very volatile methyl chloride. The product obtained in this way contained about 5 per cent. of monomethyl-aniline, but no other admixtures. Dimethylaniline is now always manufactured by heating together a mixture of aniline hydrochloride, aniline, and methyl alcohol.[1] The methyl alcohol employed must be quite

The former product is saponified by boiling with dilute hydrochloric acid, which converts it into acetic acid and methyl-aniline hydrochloride. Another method of separating aniline from its mono- and di-methyl-derivatives is referred to in the footnote on page 76. Methyl-aniline can be re-formed by treating its nitroso-derivatives with tin and hydrochloric acid.

[1] The aniline must be free from toluidine and impurities insoluble in hydrochloric acid; and the methyl alcohol employed must be quite free from ethyl alcohol and acetone, the latter of which not only reduces the yield, but gives a product unsuitable for the preparation either of methyl violet or malachite green, owing to the formation of a base of the formula $CH_2(C_6H_4.N(CH_3)_2)_2$. 93 parts of aniline are used, of which 18 are saturated

free from ethyl alcohol and acetone, the latter of which not only reduces the yield, but gives a product unsuitable for the preparation either of *methyl-violet* or *malachite-green*, owing to the formation of a base of the formula :—$CH_2(C_6H_4.N(CH_3)_2)_2$.

Dimethylaniline is a colourless oily liquid, solidifying at 0°·5 and boiling at 192°. It has a sharp basic odour, and forms uncrystallisable salts. It unites with methyl iodide, with energy at the ordinary temperature, to form the iodide of trimethyl-phenylammonium, which breaks up again into its constituents on distillation, but by reaction with argentic oxide yields trimethyl-phenyl-ammonium hydroxide, $Me_3PhN.OH$, a crystalline, very deliquescent, corrosive, and very bitter base.

With bleaching-powder solution, dimethylaniline merely gives a pale yellow coloration, a reaction by which any contamination by aniline or mono-methylaniline can be detected, as these bases give a violet colour with the same reagent (page 45). Mild oxidising agents, such as chloranile, carbon oxychloride, and cupric chloride, convert the methylaniline into *methyl violet* (Part I. page 234). With acid chlorides and aldehydes, it yields complex compounds. Thus with benzaldehyde it gives tetramethyl-paradiamido-triphenylmethane, and the corresponding hydroxide or carbinol, $C_6H_5.[N(CH_3)_2]_2.OH$, obtained from this by oxidation, is the base of *malachite* or *benzaldehyde green* (Part I. page 241). By reaction with diazobenzene chloride, dimethylaniline is converted into dimethyl-amido-azobenzene, $C_6H_5.N_2.C_6H_4.N(CH_3)_2$, or *butter yellow;* while with diazobenzene-sulphonic acid it yields *helianthin* or *methyl-orange* (Part I. page 188).

Paranitroso-dimethylaniline, $C_6H_4(NO).N(CH_3)_2$, is produced by the action of nitrite of sodium or nitrite of amyl on dimethyl-aniline.[1] It is manufactured on a large scale for the production

with hydrochloric acid and 75 parts of methyl alcohol. The excess of methyl alcohol, and comparatively small quantity of hydrochloric acid, tend to produce a purer oil. With more hydrochloric acid, the reaction takes place at a lower temperature, but there is a danger of forming toluidine. The mixture is heated at first to a temperature of 270°, at a pressure not exceeding 27 atmospheres. When the reaction is complete, in about 15 hours, the pressure decreases without the temperature being reduced (Schoop, *Chem. Zeit.*, xi. 253 ; *Jour. Soc. Chem. Ind.*, vi. 436).

[1] Ten parts of dimethyl-aniline are dissolved in 50 of strong hydrochloric acid and 200 of water, and to the cold solution is gradually added a solution of 5·7 parts of sodium nitrite in 200 of water, when the hydrochloride of the nitroso-compound is obtained as a body crystallising in yellow needles, from which the free base is obtained by treatment with potassium carbonate and solution in ether.

of *methylene-blue*, *indophenol*, and *toluylene-red* (Part I. pages 258, 285). It crystallises in large green plates or tables, soluble in ether. By oxidation with potassium permanganate or ferricyanide, it is converted into paranitro-dimethylaniline, $C_6H_4(NO_2).N(CH_3)_2$, which forms long, sulphur-yellow needles, melting at 162°–163°. When boiled with caustic alkali, nitroso-dimethylaniline is completely split up into dimethylamine, $H.N(CH_3)_2$ (which may, by this reaction, readily be obtained pure), and nitrosophenol or quinonoxime, $C_6H_4O(NOH)$ (Part I. page 157).

Commercial Dimethylaniline usually contains more or less aniline and monomethyl-aniline. By the entrance of methyl into the benzene-nucleus, more or less dimethyl-toluidine, $C_6H_4(CH_3).N(CH_3)_2$, and higher homologues are usually present in addition. Hence the dimethylaniline of commerce usually boils between 198° and 205°. The smaller the range in the boiling-point the better the sample.

The presence of aniline and monomethyl-aniline is indicated by the rise of temperature produced on treating 5 c.c. of the dry oil with an equal measure of acetic anhydride. This is stated to be 0°·815 C. for each unit per cent. of monomethylamine present. For small percentages this appears to be fairly correct, but with a product actually containing 30 per cent., an excess of over 7 per cent. is said to be indicated. A serious objection to the method is that it wholly fails in presence of aniline. But the presence of aniline can be recognised by mixing a few drops of the oil with a few drops of ether, and adding one drop of strong sulphuric acid, when, if aniline be present, its sulphate will separate as a white precipitate.

A more plausible method is that of Nölting and Boasson (*Ber.*, x. 795), based on the different behaviour of the bases with nitrous acid,[1] but the results yielded in practice have been found

[1] When aniline hydrochloride is treated in cold solution with sodium nitrite, it yields diazobenzene chloride, while dimethylaniline is converted into the hydrochloride of its nitroso-derivative (page 75). Both these bodies are freely soluble in water, while monomethyl-aniline is converted by the same treatment into the non-basic methylaniline-nitrosamine, which can be extracted by agitating the liquid with ether. If this reaction occurred in its simplicity, the monomethyl-aniline could be estimated from the weight of the nitrosamine left on evaporating the ethereal solution. But when this is distilled in a current of steam, in which the nitrosamine is volatile, a considerable quantity of nitrophenyl-methylnitrosamine, $C_6H_4(NO_2).N(NO)(CH_3)$, remains as a residue. This body is clearly produced by the oxidation of the nitrosamine, and direct experiment shows that pure monomethyl-aniline, on treatment with excess of nitrous acid, is converted

unreliable by Reverdin and de la Harpe. These chemists recommend (*Chem. Zeit.*, xiii. 387, 407; *Jour. Soc. Chem. Ind.*, viii. 84), for the estimation of the aniline and methyl-aniline conjointly, acetylisation of the bases, and estimation of the excess of acetic anhydride by titration with alkali; and for the estimation of the aniline, diazotising and treating the product with beta-naphthol disulphonic acid.

At ordinary temperatures acetic anhydride has no action on dimethylaniline, but on prolonged heating tetramethyl-diamido-phenylmethane is formed in considerable quantity, if the reagent be in excess. Monomethyl-aniline is converted into methyl-acetanilide, $C_6H_5.N(CH_3)(C_2H_3O)$, and aniline in the cold yields acetanilide, $C_6H_5.NHC_2H_3O$, but on heating more or less diacetanilide, $C_6H_5.N(C_2H_3O)_2$, is produced. To avoid the formation of these secondary products the following method of working is recommended:—From 1 to 2 grammes weight of the sample is mixed as rapidly as possible with an accurately known quantity (about twice its weight) of acetic anhydride, in a small flask fitted with a reflux condenser. After standing for half an hour at the ordinary temperature, 50 c.c. of water should be added, and the flask heated on the water-bath for fifty minutes to effect the conversion of the excess of acetic anhydride into acetic acid. The liquid is then cooled, diluted to a known volume, and an aliquot part titrated with standard caustic alkali, using phenolphthaleïn as an indicator.[1] By this means the excess of acetic anhydride, $C_4H_6O_3$, is ascertained, and the difference between the amount so found and that employed is the weight which has reacted with the *aniline* and *methyl-aniline* contained in the sample. 51 parts of acetic anhydride consumed in the reaction correspond to 107 of base in terms of *methyl-aniline*, and the percentage of base thus found (*a*) is calculated and recorded.

The *aniline* itself is determined as follows:—From 7 to 8 grammes of the sample is dissolved in hydrochloric acid (28 to 30 c.c.), and diluted with water to 100 c.c. 10 c.c. of this solution

into it, to the exclusion of the simple nitrosamine. As the molecular weights of the two bodies are materially different (181 : 136), the indefinite character of the reaction prevents the accurate determination of the monomethylamine (Reverdin and de la Harpe, *Chem. Zeit.*, xiii. 387, 407; *Jour. Soc. Chem. Ind.*, viii. 84).

[1] H. Giraud (*Bull. Soc. Chim.*, 1889, ii. 142) modifies this process by employing the acetic anhydride dissolved in ten times its volume of dimethyl-aniline. 10 c.c. of this solution is added to 1 gramme of the sample. After standing for one hour in a corked flask, water is added, and the liquid (boiled for some time and) titrated with standard baryta-water or phenolphthaleïn.

is further diluted with water and cooled by ice. The solution is then diazotised by adding a solution of sodium nitrite in quantity sufficient to react with the whole of the sample if it consisted of aniline solely. A solution of the sodium salt of betanaphthol-disulphonic acid known as "Salt R" (Part I. page 194) is meanwhile prepared of a strength approximately corresponding to 10 grammes of naphthol per litre, and its precipitating power is calculated from its known strength, or exactly ascertained by experiment with pure aniline.

A measured quantity of this solution is then treated with excess of sodium carbonate, and to it the ice-cold solution of the diazotised sample is slowly added. Common salt is then added till a precipitate ceases to form, when the liquid is filtered, and portions of the filtrate are tested with salt R and the diazo-solution respectively, to ascertain which of these two is present in excess. Another experiment is then made with suitably varied volumes, until after a few trials exact precipitation of the colouring matter is attained without sensible excess of either the naphthol or diazo-solution. The reactions which occur are as follow :—

$$C_6H_5.NH_2,HCl + HNO_2 = C_6H_5N : N.Cl + 2H_2O \text{ ; and}$$
$$C_6H_5.N_2.Cl + C_{10}H_5(OH)(SO_3Na)_2 = HCl + C_6H_5.N_2.C_{10}H_4(OH)(SO_3Na)_2.$$

From these formulæ, and the volumes of the two solutions required for exact reaction, the weight of aniline present can be calculated. 1 gramme of salt R will react with 0·2672 gramme of *aniline*. The percentage of aniline thus found (b) is multiplied by 1·15 ($=\frac{107}{93}$), which gives its equivalent in methyl-aniline, and this (c) subtracted from the sum of aniline and methyl-aniline in terms of methyl-aniline found by the acetylisation process (a) gives the percentage of real *methyl-aniline* (d) present. The *dimethyl-aniline* is determined by difference.

In the case of a sample of known composition, Reverdin and de la Harpe obtained the following satisfactory results by the foregoing process :—

	Present.		*Found.*	
Aniline, . .	10·42	per cent.	10·30	per cent.
Monomethylaniline,	10·97	„	11·16	„
Dimethylaniline (by difference), .	78·61	„	78·54	„
	100·00	„	100·00	„

The presence of monomethylaniline is more objectionable in diamethylaniline intended for the manufacture of green than in that to be used for violet. Schoop (*Chem. Zeit.*, xi. 254) states that

the proportion seldom exceeds 2 per cent., and that the best qualities of dimethylaniline are nearly or quite free from it. When present, monomethylaniline can be removed by shaking the oil with a small quantity of dilute sulphuric acid, or by boiling with acetic acid for two hours.

DIETHYLANILINE. $C_6H_5.N(C_2H_5)_2$.

This base is best prepared by heating one molecule of aniline hydrobromide with 10 per cent. in excess of one molecule of ethyl alcohol to 145° for 8 or 10 hours. Nearly the theoretical yield is obtained. The base boils at 213°·5. Diethyl-orthotoluidine and diethyl-paratoluidine may be obtained by exactly similar means.

DIPHENYLAMINE. PHENYLANILINE. $C_6H_5.NH.C_6H_5$.

This base is obtained by heating aniline with the hydrochloride or other salt of aniline.[1] Diphenylamine crystallises in small white plates, having an agreeable flowery odour and burning taste. It melts at 54°, and boils at 302° C. (Graebe). It is almost insoluble in water, but readily in alcohol, ether, benzene, and aniline. Diphenylamine has very feeble basic properties. The *hydrochloride* is a white crystalline powder, which turns blue in the air, and is decomposed by water. The most characteristic reaction of diphenylamine is the deep blue colour produced by adding a trace of nitric acid to its solution in strong sulphuric acid. The reaction, which is very delicate, is employed as a test for nitric acid.

Commercial diphenylamine should be pale yellow, melt not much below 54°, be free from unpleasant odour and oily matters, and give no violet coloration with bleaching powder. It is used for making *diphenylamine blue*, *aurantia*, and *orange IV.*

Methyl-diphenylamine, $C_6H_5.N(CH_3)C_6H_5$,[2] boils at 282°, and gives various colour-reactions with oxidising agents. In dilute sulphuric acid it dissolves to form a liquid of the colour of solution of potassium permanganate.

[1] Six parts of aniline and 7 of aniline hydrochloride are heated to 250° under a pressure of 4 or 5 atmospheres for 24 hours. The ammonia formed is allowed to escape at intervals to prevent reconversion of the diphenylamine into aniline. The product is treated with warm hydrochloric acid and a large quantity of water, which dissolves any unchanged aniline hydrochloride, and decomposes the hydrochloride of diphenylamine, which latter base separates out and is purified by distillation.

[2] Made on a large scale by heating a mixture of 100 parts of diphenylamine, 68 of hydrochloric acid (sp. gr. 1·17), and 2 parts of methyl alcohol for 10 hours, to 200°–250° at a pressure of 15 atmospheres. The product is treated with caustic soda, and the separated base distilled and shaken with twice its measure of strong hydrochloric acid. The hydrochloride of diphenylamine separates in the solid form, while that of the methyl-derivative forms a liquid, which is decomposed by adding a large quantity of water.

Warm nitric acid converts *diphenylamine* and *its methyl-derivative* into $C_6H_2(NO_2)_3.NH.C_6H_2(NO_2)_3$, hexanitro-diphenylamine, the ammonium salt of which constitutes the colouring matter known as *aurantia* (Part I. page 156).

Para-amido-diphenylamine results from the reduction of phenyl-amido-azobenzene, nitro-phenylamine, or *tropæolin OO* (Part I. pages 181, 189, 190, 213).

TRIPHENYLAMINE. DIPHENYLANILINE. $(C_6H_5)_3N$.

This body is formed by the action of bromobenzene on dipotassium aniline. It is a neutral body, melting at 127°, and crystallising from ether in monoclinic pyramids. It forms no isonitrile, picrate, nor acetyl-compound, but yields iodide of triphenyl-methyl-ammonium on treatment with methyl iodide. Its solution in glacial acetic acid is coloured green on adding a little nitric acid, but with sulphuric acid it gives a violet coloration changing to blue.

Amidophenols.

By the reduction of the nitrophenols, corresponding amido-compounds are obtained. These bodies may also be prepared by heating either of the three isomeric amido-hydroxybenzoic acids, $C_6H_3(NH_2)OH.COOH$, with caustic baryta.

In the amidophenols the acid character of the phenols is neutralised by the presence of the amido-groups, so that they only yield salts with acids; but as phenols they are still capable of yielding alkyl-derivatives (*e.g.*, anisidine), while the hydrogen of their amido-groups may be replaced for acetyl, &c., as in phenacetin.

The amidophenols form colourless crystalline scales or plates, which are very readily oxidisable on exposure to air, with blackening and formation of resinous products, especially if impure. On the other hand, their hydrochlorides are relatively stable, and often capable of sublimation. The solution of *paramidophenol* hydrochloride is coloured first violet and then green by solution of bleaching powder, quinone chlorimide, $C_6H_4O(NCl)$, being formed; while with chromic acid mixture, and other oxidising agents, it yields quinone, $C_6H_4O_2$. Treatment with sulphuretted hydrogen and ferric chloride converts it into compounds of the *methylene-blue* group (Part I. page 285).

The formyl- and acetyl-derivatives of the amidophenols are converted with great facility into anhydro-bases. Thus ethenyl-amidophenol, *a basic liquid boiling at 200° to 201°*, is obtained by boiling ortho-amidophenol with acetic anhydride.

$$C_6H_4(OH).NHC_2H_3O = C_6H_4\langle{}^{N}_{O}\rangle C.CH_3 + H_2O.$$

When this body is heated with dilute acids, the reverse action occurs, acetyl-orthoamidophenol being formed.

The methyl esters of the amidophenols (anisidines or amido-anisols), and the corresponding ethyl esters (phenethidines or amidophenatols), are bases resembling aniline, and are employed for producing certain azo-dyes (*e.g.*, *anisol red*, *phenatol red;* Part I. page 192). The acetyl-derivatives of these esters are used in medicine under the names of *metacetin* and *phenacetin* (see below).

The following table shows the characters of the isomeric amidophenols and their derivatives :—

	Ortho- 1:2		Meta- 1:3		Para- 1:4	
	Melting-Point.	*Boiling-Point.*	*Melting-Point.*	*Boiling-Point.*	*Melting-Point.*	*Boiling-Point.*
	°	°	°	°	°	°
Amidophenol (page 80), $C_6H_4\begin{cases}OH\\NH_2\end{cases}$	170	sublimes.	...	...	184	...
Acetyl-derivative (page 80), $C_6H_4\begin{cases}OH\\NH(COCH_3)\end{cases}$	201	...	...	...	179	...
Methyl-ester (Anisidine), $C_6H_4\begin{cases}O(CH_3)\\NH_2\end{cases}$	...	228	...	251	56	246
Ethyl-ester (Phenethidine), $C_6H_4\begin{cases}O(C_2H_5)\\NH_2\end{cases}$	...	229	...	180–205 (at 100 mm.)	...	253
Methacetin (page 85), $C_6H_4\begin{cases}O(CH_3)\\NH(COCH_3)\end{cases}$	84	204	...	...	127	...
Phenacetin (page 81), $C_6H_4\begin{cases}O(C_2H_5)\\NH(COCH_3)\end{cases}$	70	...	97	...	135	...
Amidophenacetin. Phenocoll (page 85), $C_6H_4\begin{cases}O(C_2H_5)\\NH(CO.CH_2.NH_2)\end{cases}$	...	...	...	...	100·5	...

PHENACETINS. ACET-PHENETHIDINES.

$$C_6H_4\begin{cases}O(C_2H)\\NH(CO.CH_3)\end{cases}$$

The bodies of this formula have recently acquired some reputation as antipyretics and analgesics.

The phenacetins are prepared by ethylating the corresponding mono-nitrophenols, thus obtaining the isomers of the formula $C_6H_4(NO_2).OC_2H_5$. On treatment with zinc or iron and hydro-

chloric acid, these are reduced to the corresponding phenethidines, $C_6H_4(NH_2).OC_2H_5$, which are purified and acetylised by heating with glacial acetic acid for some hours, the products being recrytallised from water.

Of the three isomeric phenacetins, the *meta*-compound is unimportant. It forms tasteless and odourless scales, melting at 96°.

Para-acetphenethidine is the official variety in the *German* and *British Pharmacopœias* (1890). It forms white, odourless, tasteless, glistening scaly crystals. It requires 1400 parts of cold, or 70 parts of boiling, water for solution, and is soluble to a notable extent in chloroform. Its solution in 16 parts of alcohol is precipitated by the smallest addition of water. The crystals melt at 135°.

Ortho-acetphenethidine forms brilliant white, very light spangles, without taste or odour, and melting at 70° C. It is very slightly soluble in cold, but more readily in hot, water, separating again on cooling. It dissolves in about three parts of rectified spirit, and abundantly in chloroform.

Besides the differences in their melting-points and solubilities, para- and ortho-phenacetin are distinguished by their behaviour when boiled for several hours with dilute sulphuric acid (sp. gr. 1·26). When thus treated, the para-compound yields acetic acid and sparingly soluble sulphate of phenethidine. Orthophenacetin, on the other hand, is not decomposed by the same treatment, requiring the action of acid of 1·575 specific gravity for two hours at 90° to effect its saponification.[1] If in either case the acid liquid be diazotised, and then treated with an ammoniacal solution of naphthol-disulphonic acid, a fine red-yellow colour will be obtained if paraphenacetin was employed, while with the ortho-compound a cherry-red coloration is produced. In either case the colouring matter may be precipitated by brine.

This formation of an azo-colouring matter may be employed to detect the phenacetins in urine and other organic liquids. The urine is evaporated to dryness, and the residue treated with hot alcohol. The solution is filtered, evaporated, and the residue boiled for two hours with dilute sulphuric acid (sp. gr. 1·26) under a reflux condenser. The resultant solution is cooled to 5° or 6° C., treated with a 1 per cent. solution of sodium nitrite for five minutes, and then poured into a solution of napthol-disulphonic acid in excess of ammonia, taking care that the mixture remains

[1] S. Lüttke detects orthophenacetin by boiling 15 grammes of the sample with 25 grammes of dilute hydrochloric acid, when ortho-phenethidine hydrochloride is formed, from which the free base may be separated by caustic soda, and its boiling-point (given by Lüttke as 242°·5) determined. The hydrochloride gives a blood-red coloration with ferric chloride.

alkaline. If either modification of phenacetin be present in the urine a characteristic coloration will be produced, from the intensity of which the amount of phenacetin may be estimated.

For medicinal use, phenacetin is said to present considerable advantages over antipyrine, and especially over antifebrin (acetanilide), for while the latter body is decomposed in the system with formation of aniline, which has marked toxic properties, phenacetin yields phenethidine, $C_6H_4(OC_2H_5).NH_2$, and amidophenol, $C_6H_4(OH).NH_2$, which are said to be harmless. Paraphenacetin, in doses ranging from 8 to 20 grains for adults, and from 2 to 3 grains for children, is said to be a valuable anti-pyretic and anti-neuralgic, without producing nausea, vomiting, cyanosis, or disagreeable after-effects. Being nearly insoluble, it is best given in the form of powders. The dose of orthophenacetin required to produce the same effect is larger than that of the para-compound, which is that of the *British* and *German Pharmacopœias*.

According to Reuter (*Pharm. Zeit.*, 1891, page 185) phenacetin is liable to contain unconverted *para-phenethidine*, which appears to be poisonous in very small doses, if taken for some time, producing nephritis and albuminuria. To detect the impurity, Reuter melts 2½ grammes of chloral hydrate at 100°, and adds 0·5 gramme of the sample. On agitation the phenacetin dissolves, and, if pure, the solution will remain colourless when heated on the water-bath for five minutes, though after longer heating it will assume a rose tint. In presence of para-phenethidine, an intense coloration, ranging from red-violet to blue-violet, is produced in two or three minutes at most.

S. Lüttke detects *diamidophenols* or *diamidophenatols* in phenacetin by grinding 0·5 gramme of bleaching powder to a fine paste with hydrochloric acid, and adding about 0·03 of the sample, when a red colour will be produced.

The lower price of *acetanilide*, and its close physical resemblance to phenacetin, have suggested the possibility of the partial or complete substitution of the former body for the latter, and a flagrant instance of such a practice is actually on record (*Pharm. Jour.*, [3], xxi. 377). The presence of 5 per cent. of acetanilide lowers the melting-point of the sample to 127°–128°.

H. Schwartz (*Pharm. Jour.*, [3], xviii. 1085) recommends that 1 gramme of the suspected sample should be heated with 2 c.c. of caustic soda solution, a fragment of chloral hydrate or a few drops of chloroform added, and the mixture again gently heated. With phenacetin the odour is aromatic and not disagreeable, but in presence of acetanilide, the penetrating and repulsive smell of

phenyl-carbamine, $C_6H_5.NC$, is produced. On boiling the sample with caustic soda solution, oily drops of aniline separate if acetanilide be present in considerable quantity. If the cooled liquid, together with the separated globules, be shaken with ether, and the ether separated and evaporated, the residue when dissolved in water and treated with a drop of carbolic acid, and a clear solution of bleaching powder added, gives a blue-green coloration changed to onion-red by hydrochloric acid, and restored by ammonia. (See also *Jour. Soc. Chem. Ind.*, vii. 772.)

For the detection of acetanilide in phenacetin, M. J. Schröder recommends that 0·5 gramme of the sample should be boiled with 8 c.c. of water, and the liquid filtered when cold from the recrystallised phenacetin. The filtrate is boiled with a little potassium nitrite and dilute nitric acid, a solution of mercurous nitrate containing a little nitrous acid added, and the whole again boiled. A red colour will be obtained if the proportion of acetanilide in the sample exceeds 2 per cent.

If 1 gramme of a mixture of equal parts of phenacetin with acetanilide be shaken with 200 c.c. of water, the whole of the acetanilide goes into solution together with 0·130 gramme of phenacetin, while the remainder of the phenacetin remains insoluble. If this be separated, its weight, when corrected by an addition of 0·130, will represent the phenacetin present in 1 gramme of the sample (*Pharm. Jour.*, [3], xxi. 377).

Phenacetin has been made official in the *German Pharmacopœia* (1890), the maximum dose being 1 gramme. It is stated to melt at 135°, and dissolve in 1400 parts of cold, 70 of boiling, water, and 16 of spirit to form neutral solutions. It is distinguished from exalgin and antifebrin by boiling 0·1 gramme for a minute with 1 c.c. of hydrochloric acid, adding 10 c.c. of water, filtering, and adding to the filtrate 3 drops of a 3 per cent. solution of chromic acid, when a ruby-red colour will be gradually developed. (See *Pharm. Jour.*, [3], xxi. 978.) Strong sulphuric acid should dissolve phenacetin without becoming coloured, while a saturated solution, if free from phenol and acetanilide, will not become turbid on adding bromine-water. The description of phenacetin in the *British Pharmacopœia additions* (1890) closely corresponds with the above. The dose is from 5 to 10 grains.

Methyl-phenacetin, $C_6H_4(O.C_2H_5).N(CH_3)(C_2H_3O)$. This body is prepared by treating para-phenacetin in xylene solution with sodium, and causing the resultant sodium-derivative to react with methyl iodide (*Pharm. Jour.*, [3], xxi. 81). The new product distils at about 300° C. as an oil, which crystallises on standing. It may be purified by recrystallisation from alcohol

or ether, when it forms colourless crystals, moderately soluble in water, and having marked narcotic as well as antipyretic characters.

Amido-paraphenacetin, $C_6H_4(O.C_2H_5).NH(CO.CH_2.NH_2)$. The *hydrochloride* of this base is readily soluble in water and alcohol, and has been introduced, under the name of "*phenocollum hydrochloricum*," as an antipyretic and antirheumatic. Prolonged boiling with alkalies splits it into para-phenethidine and glycocine.

Formyl-paraphenethidine, $C_6H_4(O.C_2H_5).NH(CO.H)$, though having a constitution similar to acet-phenethidine, appears to have no antipyretic properties, but has been suggested as an antidote in cases of poisoning by strychnine.

Methacetin is the commercial name of para-acet-anisidine, $C_6H_4(O.CH_3).NH.C_2H_3O$. It is, consequently, the lower homologue of phenacetin (page 81). It forms a crystalline powder or small lustrous scales or plates, odourless, but of a faintly bitter taste. It melts at 127° C., and at a higher temperature boils and distils unchanged. It dissolves in 526 parts of cold, or 12 of boiling, water, and is easily soluble in alcohol, acetone, chloroform, and dilute acid and alkaline liquids. It is less soluble in benzene, and only with difficulty in ether, carbon disulphide, petroleum spirit, and oil of turpentine, but dissolves freely, on warming, in glycerin and fixed oils. In its general reactions and physiological effects, metacetin closely resembles phenacetin, though according to some authorities it has a less powerful, and according to others a more powerful, action. Its efficacy in cases of neuralgia and rheumatism is said to greatly exceed phenacetin, from which it may be distinguished by its physical characters, or by heating it with a quantity of water insufficient for its solution. When thus treated, methacetin melts and solidifies again on cooling, whereas phenacetin undergoes no apparent change. 1 c.c. of hydrochloric acid dissolves 0·1 gramme of methacetin very easily, whereas the same quantity of phenacetin is mainly undissolved.

DIAMIDOPHENOLS. $C_6H_3(OH)(NH_2)_2$.

These bodies are weak bases, forming salts which crystallise well and give aqueous solutions which turn brown in the air; and are coloured an intense violet or dark red by potassium bichromate, ferric chloride, or bleaching powder.

TRIAMIDOPHENOL. $C_6H_2(OH)(NH_2)_3$.

This body is an unstable base resulting from the complete reduction of picric acid, $C_6H_2(OH)(NO_2)_3$, in acid solutions. If alkaline reducing agents be employed, the action does not proceed beyond the formation of dinitro-amido-phenol or picramic acid, $C_6H_2(OH)(NH_2)(NO_2)_2$ (see Part I, page 143).

A dilute solution of triamidophenol is coloured deep blue by ferric chloride.

Phenylene-diamines. Diamidobenzenes.

Three modifications of phenylene-diamine or diamido-benzene, $C_6H_4(NH_2)_2$, are known, differing from each other in properties according to the positions of the amido-groups, thus:—

	Ortho-Compound. 1 : 2	Meta-Compound. 1 : 3	Para-Compound. 1 : 4
Appearance, . . .	Tablets or plates.	Crystalline mass.	Tablets or small plates.
Melting-point, . . .	102°–103°	63°	140°
Boiling-point, . . .	252°	287°	267°
Characters of hydrochloride,	Groups of radiating needles; readily soluble.	Concentrically arranged crystals.	Readily soluble tablets; very sparingly soluble in hydrochloric acid.
Reaction in neutral solution with sodium nitrite,	Separation of amido-azo-phenylene as a colourless oily liquid.	Yellow or brown coloration, or precipitate of triamidoazobenzene.	No reaction.

Ortho-phenylene-diamine is distinguished from its isomerides by its reaction with sodium nitrite, and by the separation of ruby-red needles on adding ferric chloride to the solution of its hydrochloride. On treating an alcoholic solution of the base with a drop of phenanthraquinone dissolved in glacial acetic acid, and boiling for a short time, a bright yellow precipitate of diphenylene-quinoxaline, $C_{20}H_{12}N_2$, is formed. It consists of small needles which are coloured a deep red by strong hydrochloric acid, and its production affords the most delicate reaction for ortho-phenylenediamine. Its isomerides do not give the reaction, but its homologue, ortho-toluylenediamine, behaves similarly.

Meta-phenylene-diamine may be prepared by the reduction of meta-dinitrobenzene (Part I. page 178, footnote). It often remains in a state of superfusion for some time, but is instantly solidified by adding a crystal of the solid substance. Metaphenylene-diamine is sparingly soluble in water, the solution being alkaline in reaction. It is readily soluble in ether, and may be extracted by this solvent from alkaline aqueous liquids. It is a di-acid base, the *hydrochloride* being $C_6H_4(NH_2)_2,2HCl$. The reaction of metaphenylenediamine with sodium nitrite is characteristic and extremely delicate. It is due to the formation of *Bismarck* or *phenylene brown* (Part I. page

180), and by means of it one part per million of nitrous acid can be detected in water.

Metaphenylenediamine possesses marked poisonous properties, its physiological action resembling that of the leucomaines and ptomaines. Dubois and Vignon (*Compt. Rend.*, cvii. 533) experimented on dogs, and found that a dose of 0·1 gramme per kilogramme of the animal produced salivation, vomiting, diarrhœa, abundant excretion of urine at intervals, and death by coma in twelve to fifteen hours. Besides these severer symptoms, all those of intense influenza were produced, such as acute coryza and sneezing, coughing, and extreme depression.

PARA-PHENYLENE-DIAMINE occurs in aniline tailings (page 67). It may be prepared by the reduction of paranitracetanilide. It is but slightly soluble in water, but readily in alcohol and ether. When heated with dilute sulphuric acid and manganese dioxide it yields quinone, $C_6H_4O_2$, which reaction distinguishes it from its isomerides. On passing sulphuretted hydrogen through a solution of the hydrochloride, and then adding ferric chloride, *thionine* or *Lauth's violet* is formed (Part I. page 285).

Para-phenylenediamine possesses poisonous properties similar to those of meta-phenylenediamine, but death occurs more rapidly than with the latter base. It also exerts a special action on the eye, which is gradually forced out of its orbit by the swelling of the conjunctiva or intra-orbital cellular tissue; while the lachrymal glands are blackened by a deposit of pigment (compare "Toluylene-diamines").

Dimethyl-paraphenylenediamine, $H_2N.C_6H_4.N(CH_3)_2$, may be obtained by the reduction of nitrosodimethyl-aniline or of *helianthin* (Part I. pages 188, 211). A neutral solution of the hydrochloride is coloured a beautiful purple by ferric chloride; and on treating it with a hydrochloric acid solution of sulphuretted hydrogen, and then adding ferric chloride till the smell of sulphuretted hydrogen has disappeared, a fine blue coloration is obtained, due to the formation of *methylene blue* (Part I. page 285). This reaction is the most delicate test for

TOLUYLENE-DIAMINES. DIAMIDOTOLUENES. $C_6H_3(CH_3)(NH_2)_2$.

These bases closely resemble the phenylene-diamines. The *ortho-para*-modification ($CH_3 : NH_2 : NH_2 = 1 : 2 : 4$) is obtained by the reduction of ordinary dinitrotoluene. It melts at 88°, is used for the production of *toluylene red* and *toluylene orange*. The 1 : 3 : 4 (*meta-para*) modification is obtained by nitrofying acet-paratoluide, saponifying, and reducing.[1] Janovsky (*Jour. Soc. Chem. Ind.*,

[1] This modification appears to be identical with the paratoluylenediamine isolated by Hell and Schoop from aniline tailings (*Berichte*, xii. 723).

ix. 383) gives the following table of reactions of neutral or slightly acid solutions of the two isomeric toluene-diamines:—

Reagent.	α-Toluylene-diamine. $CH_3:NH_2:NH_2=1:2:4$	β-Toluylene-diamine. $CH_3:NH_2:NH_2=1:3:4$
Ferric chloride.	No change at first; after standing for a long time an orange coloration.	Wine-red coloration.
Potassium bichromate.	Yellowish-brown coloration.	Reddish-brown precipitate.
Potassium ferricyanide.	Olive-green crystalline plates.	Dark-red coloration.
Bromine water.	Yellowish-white precipitate.	Brown flocks and magenta-red solution.
Platinic chloride.	Yellowish-brown coloration.	Reddish-brown precipitate.
Auric chloride.	Brown precipitate.	Red solution with blue reflex and metallic mirror in the cold.
Potassium nitrite.	In very dilute solutions a golden-brown coloration; in concentrated a brown precipitate.	No coloration, but a salmon-coloured precipitate.
Solution of bleaching powder.	Reddish-brown coloration and then a light brownish-yellow precipitate.	Dark-red coloration, then an olive-green precipitate.

The foregoing reactions are available, even in presence of other substances, for the detection and identification of the toluylene-diamines, which often result from the reduction of azo-dyes.

The toluylene-diamines are powerful poisons (compare "Metaphenylenediamine," page 87).[1]

Benzidine. Dipara-amido-diphenyl.

$$C_{12}H_{12}N_2=NH_2.C_6H_4.C_6H_4.NH_2\ (1,\ 4\ :\ 1,\ 4).$$

This body is obtained by the reduction of diparanitro-diphenyl, $NO_2.C_6H_5.C_6H_4NO_2$, by nascent hydrogen (tin and hydrochloric acid). A readier method of preparation is the following:—An alcoholic solution of 10 parts of azobenzene, $C_6H_5.N:N.C_6H_5$,

[1] Engel and Kiener (*Compt. Rend.*, cv. 465; *Jour. Chem. Soc.*, liv. 81) find the symptoms to vary considerably according to the time required to produce death, which ranges from a few hours in acute cases to several weeks in chronic cases. When death ensues in a few days, there is always icteria, and often hæmoglobinuria, and the urine is loaded with fat and yellow and brown pigment-granules, which sometimes contain iron. This ferruginous pigment accumulates in the spleen and marrow, and seems to be formed from the hæmoglobin in the protoplasm from the cellules, and not from the red corpuscles.

is treated with a solution of 3½ parts of tin in concentrated hydrochloric acid, and the liquid warmed for some time. Hydrazobenzene, $C_6H_5.NH.NH.C_6H_5$, is formed, which by intramolecular change is converted into benzidine (dihydrochloride). Some of the isomeric ortho-para-diamidodiphenyl is simultaneously formed, and a portion of the azobenzene is reduced to aniline, $C_6H_5.NH_2$. The alcohol is distilled off, the residue dissolved in water, and sulphuric acid added. The nearly insoluble benzidine sulphate is precipitated, while the sulphates of the isomeric base and of aniline remain in solution. The precipitate is washed with dilute hydrochloric acid (to remove tin salts) and treated with ammonia, the liberated benzidine being crystallised from dilute alcohol. Benzidine is also produced by treating azobenzene with sulphur dioxide. Benzidine is manufactured on a large scale by heating nitrobenzene with caustic soda, a little alcohol, and the proportion of zinc-dust theoretically sufficient to reduce it to hydrazobenzene. The product is washed with cold dilute hydrochloric acid to remove oxide of zinc. On subsequently heating it with dilute hydrochloric acid, it is converted into benzidine dihydrochloride.

Benzidine forms large pearly plates, which are colourless when pure, but rapidly turn red on exposure to the air. It melts at 122°, and boils with partial decomposition above 360°. Benzidine is very sparingly soluble in cold, but readily in boiling, water, and is easily soluble in alcohol and ether.

Benzidine is a well-defined di-acid base, forming crystallisable salts. The sulphate is very sparingly soluble in water, even when boiling.

On adding potassium bichromate to a concentrated solution of benzidine hydrochloride, a deep blue crystalline precipitate, containing $C_{12}H_8(NH_2)_2CrO_4$, is immediately formed. The same precipitate is formed on warming, even in very dilute solutions.

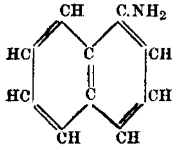
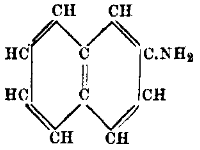
When chlorine-water is added in small quantity of a solution of benzidine hydrochloride, the liquid assumes a fine blue colour, which on further addition of chlorine-water changes to green; and ultimately, when the chlorine is in excess, a flocculent red precipitate is formed, apparently containing $C_{12}H_7Cl_3N_2O$, soluble in alcohol and ether, and forming a colourless compound on reduction. Bromine-water and a solution of bleaching powder act similarly; but in presence of a large quantity of free hydrochloric acid bromine forms tetrabrombenzidine, melting at 285°. With nitrous acid, solutions of benzidine salts react to form tetrazo-compounds which react with phenols, phenolsulphonic and carboxylic acids, amidosulphonic acids, &c., to form the important class of bodies known as "tetrazo-dyes," of

which *congo-red* is the type (Part I. page 206), and which are remarkable for dyeing cotton without a mordant.

ORTHOTOLIDINE. $NH_2.C_6H_3(CH_3).(CH_3)C_6H_3.NH_2$. This base is homologous with benzidine, and is prepared from ortho-nitrotoluene by the same process by which benzidine is prepared from nitrobenzene. It melts at 128°, and presents a close resemblance to benzidine. The tetrazo-dyes prepared from it are less readily altered by acids than are the similar dyes prepared from benzidine.

NAPHTHYLAMINES AND THEIR ALLIES.

When naphthalene, $C_{10}H_8$, is treated cautiously with nitric acid, nitronaphthalene, $C_{10}H_7(NO_2)$, is formed, and this by treatment with reducing agents is converted into amido-naphthalene or naphthylamine, $C_{10}H_7(NH_2)$. These reactions are strictly analogous to those by which aniline is prepared from benzene, and the product is known as *alpha*-naphthylamine. But by other reactions the isomeric *beta*-naphthylamine may be obtained. These two bodies differ from each other in a notable manner, as indicated in the following table :—

	Alpha-Naphthylamine.	*Beta*-Naphthylamine.
Structural Formula, .		
Melting-point, . . .	50°	112°
Boiling-point, . . .	300°	294°
Odour, ...	Disagreeable; persistent.	None.
Appearance, ...	Flat needles or prisms.	Pearly plates.
Reactions of hydrochloride in solution :—		
With ferric chloride, .	Blue precipitate.	No reaction.
With nitrous acid in alcoholic or acetic acid solution,	Yellow colour, turned crimson by hydrochloric acid.	No reaction.
With sulphanilic acid and sodium nitrite, followed by hydrochloric acid,	Red coloration.	...

α-Naphthylamine. $C_{10}H_7.NH_2$.

This base is obtained (as already stated) by the reduction of nitronaphthalene, or by heating α-naphthol with the double compound of chloride of calcium and ammonia.[1]

α-Naphthylamine has a most disgusting and persistent odour, resembling that of fæces. It turns violet or brown in the air, but when purified by sublimation this change occurs very slowly, and only on exposure to air and light. It is slightly volatile with steam.

α-Naphthylamine is nearly insoluble in water, but very soluble in alcohol and ether. It forms a series of readily-crystallisable, easily-soluble salts. On adding ammonia to a solution of the sulphate, the free base is precipitated in white silky needles.

On adding ferric chloride to a solution of α-naphthylamine, or of one of its salts, an azure blue precipitate of naphthameïn is produced, which rapidly becomes purple, but is unchanged by treatment with sulphurous acid. Other oxidising agents (*e.g.*, chromic acid, bleaching powder) produce precipitates varying in colour from blue to violet or red.

On adding an alcoholic solution of nitrous acid to a solution of α-naphthylamine in alcohol or glacial acetic acid, a yellow colour is produced, which, on adding a little hydrochloric acid, changes to an intense violet or magenta colour; or, in presence of only traces of naphthylamine, to a reddish colour.

If to a cold solution of alpha-naphthylamine sulphanilic acid and sodium nitrite be added, a red colour is produced on adding hydrochloric acid, owing to the formation of amidonaphthylazobenzene-sulphonic acid, $C_{10}H_6(NH_2).N_2.C_6H_4(SO_3H)$.

α-Naphthylamine is used for the preparation of *Magdala red* (Part I. p. 257), certain azo-dyes, and naphthalene fancy-colours on cotton.

Commercial α-naphthylamine ought to melt at 50° C., and be almost completely soluble in dilute hydrochloric acid. *Naphthalene*, the presence of which causes incomplete solubility, may be determined by distilling the acidulated solution in a current of steam, agitating the distillate with ether, separating the ethereal layer, evaporating it at a low temperature, and weighing the residue.

[1] On a large scale, α-naphthylamine is prepared in a manner very similar to that employed for the production of aniline. Nitronaphthalene is reduced by iron and hydrochloric acid at a temperature of about 50°. When the reduction is complete, milk of lime is added, and the naphthylamine distilled off by the aid of superheated steam. The crude product is purified by redistillation, when it is obtained as a nearly colourless oil, which solidifies to crystalline cakes of a greyish colour. It appears to be wholly free from β-naphthylamine, but contains an impurity which is probably 1:1′-naphthylene-diamine, $C_{10}H_6(NH_2)_2$ (O. N. Witt, *Dingl. Polyt. Jour.*, cclxv. 225).

β Naphthylamine. $C_{10}H_7.NH_2$.

This modification of amidonaphthalene is most readily obtained by heating β-naphthol under pressure with ammonia at 160°, or with the double compound of zinc chloride and ammonia at 200°–210°.

β-Naphthylamine is odourless and more stable than the α-modification. It volatilises in a current of steam, and is slightly soluble in cold, more readily in hot, water, the solution exhibiting a blue fluorescence, which, however, is not shown by β-naphthylamine salts. β-Naphthylamine gives no coloration with oxidising agents, nor with nitrous and hydrochloric acids in alcoholic solution.

Commercial β-naphthylamine ought to melt at 112° C., and be completely soluble in dilute hydrochloric acid.

TETRAHYDRO-β-NAPHTHYLAMINE. $C_{10}H_{11}.NH_2$.

This base has been introduced into medicine under the name of "Thermine." It is a colourless, slightly viscous liquid, of peculiar odour. It is a strong base, a drop soon becoming converted into a crystalline mass of the *carbonate* on exposure to air. The *hydrochloride* forms well-defined white crystals, melting at 237°, and readily soluble in water, alcohol, and amylic alcohol.

The physiological effects of thermine embrace the two strongly-marked characteristics of mydriasis (accompanied by pain) and elevation of the temperature, which latter effect has been observed to the extent of 4½° C.

Naphthylamine-Sulphonic Acids.

When treated with dilute sulphuric acid, the naphthylamines dissolve easily with formation of sulphates, but by the action of concentrated sulphuric acid at a high temperature they are converted into sulphonic acids. Thus when α-naphthylamine is heated with fuming sulphuric acid, two isomeric sulphonic acids are formed, one of which is readily soluble in water, while the other is only sparingly soluble. The latter modification crystallises in small lustrous needles, and in aqueous solution exhibits a beautiful fluorescence. Similarly, β-naphthylamine yields on sulphonation several isomeric acids. According to A. G. Green (*Ber.*, xxii. 721), at moderate temperatures (100° C.), and with ordinary sulphuric acid, the product is a mixture of α and γ acids, having their sulphonic groups in the α-position; while at a higher temperature (160°–170°) β and δ modifications are produced, having their sulphonic groups in the β-position. The ammonium salt of the β-acid is less soluble than the three isomeric salts, and by this means the β-acid can readily be isolated.

The α-naphthylamine-sulphonic acids may also be obtained by treating nitronaphthalene, $C_{10}H_7NO_2$, with fuming sul-

phuric acid, and reducing the resultant nitronaphthalene-sulphonic acid, $C_{10}H_6(NO_2)(SO_3H)$, with iron and hydrochloric acid. Two isomeric amido-sulphonic acids are obtained in this case also.

The naphthylamine-sulphonic acids are also conveniently prepared by heating the corresponding naphthol-sulphonic acids (Part I. pages 194, 207, 208) with ammonia under pressure.

Naphthylamine-disulphonic acids may be obtained by reactions similar to those described above. Two of these derivatives of β-naphthylamine are technically known as "Amido-acid R" and "Amido-acid G." The latter, or γ-acid, is not capable of reacting with diazo-compounds, but the first, or α-acid, produces colouring matters which yield colourless solutions on reduction.[1]

Naphthalene-Diamines. $C_{10}H_6(NH_2)_2$.

These bases may be formed by heating the corresponding dihydroxynaphthalenes with ammonia, by the reduction of the dinitronaphthalenes, and in other ways.

The following table exhibits their leading properties :—

Position of the Amido-Groups.	α_1, α_2	α_1, α_3	α_1, α_4	α_1, β_1	
Mode of preparation,	From α-nitro-naphthylamine by reduction, and from azo-compounds of α-naphthylamine.	From α-di-nitro-naphthalene.	From β-di-nitro-naphthalene.	By reducing azo-compounds of β-napthylamine.	From $\alpha_1 - \alpha_3$. Dihydroxy-naphthalene.
Form of crystals,	Leaves.	Needles.	Needles.	Plates.	Needles.
Melting-point,	120° C.	189°·5 C.	66°·6 C.	95° C.	189° C.
Hydrochloride,	Plates.	Needles (?).	...	Plates.	Plates.
Sulphate,	...	Needles.	...	Plates.	Needles.
Reaction of the hydrochloride with ferric chloride,	Green coloration.	Blue coloration; then blue precipitate.	Chestnut-brown precipitate.	Green, then yellow coloration; brown precipitate.	Blue coloration; then precipitate.
Action of nitrous acid,	Sol. tetrazo-compound.	Sol. tetrazo-compound.	Vermilion precipitate.	...	Sol. tetrazo-compound.
Action of the azo dye-stuffs on unmordanted cotton,	Do not dye.	Dye the fibre.	...	...	Dye the fibre.

[1] For further information respecting the naphthylamine-disulphonic acids and the naphthalene derivatives generally, see various papers by Armstrong and Wynne (*Jour.* and *Proc. Chem. Soc.*, 1890, 1891), and the article by Wynne in Thorpe's *Dictionary of Applied Chemistry*, ii. 649 *et seq.*

Amidonaphthols. $C_{10}H_6(OH)(NH_2)$.

These bodies are unstable bases obtained by the action of reducing agents on the nitro- or nitroso-naphthols, or on certain azo-dyes. The following table shows the leading differences of the principal members of the group :—

	α-Amido-α-naphthol.	β-Amido-α-naphthol.	α-Amido-β-naphthol.
Relative position of the OH and NH_2 groups.	1:4	1:2	2:1 (or 4)
Mode of formation.	Reduction of 1:4 nitro-α-naphthol melting at 164°; or of Orange I. (Part I. page 284).	Reduction of 1:2 nitro-α-naphthol melting at 128°; or of nitroso-α-naphthol.	Reduction of the nitro-β-naphthol, melting at 103°; of nitroso-β-naphthol; or of Orange II. (Part I. page 184).
Characters of free base.	Unstable.	Unstable.	Colourless scales; slightly soluble in water; oxidised in the air. Ethereal solution exhibits violet fluorescence.
Reaction on agitating alkaline solution with air.	Dirty green coloration, changing to yellow.	Permanent grass-green colour, and green scum soluble in alcohol to pure green solution. Or violet naphthoquinonimide— $C_{10}H_6\left\{\begin{matrix}NH\\O\end{matrix}\right\}$	Brown coloration.
Reaction with bromine water.	Yellowish-white needles precipitated, even in very dilute solutions.	Yellowish or green precipitate (the same with ferric chloride).	...
Characters of hydrochloride.	Long white needles or acicular plates. With bleaching powder yields $C_{20}H_{12}N_3Cl$, which separates from acetic acid solution in needles, melting at 85° and exploding at 130°.	White laminæ.	White lustrous needles; readily soluble in water, but only sparingly in dilute hydrochloric acid.
Product of oxidation with chromic acid mixture.	Theoretical yield of α-naphthaquinone.	β-naphthoquinone.	β-naphthoquinone.

Amidonaphthol-sulphonic Acids. These bodies result from the reduction of azo-derivatives of the respective diazobenzene compounds of naphthol-sulphonic acids. Thus, for instance, by treating the four known modifications of β-naphthol-monosulphonic acid with stannous chloride, O. N. Witt obtained the following amido-sulphonic acids (*Berichte*, xxi. 3468, 3489):—

1. Amido-β-naphthol-β-sulphonic acid, from Schäffer's acid (Part I. page 194).
2. Amido-β-naphthol-α-sulphonic acid, from Bayer's acid (Part I. page 194).
3. Amido-β-naphthol-δ-sulphonic acid, from Casella's acid (Part I. page 208).
4. Amido-β-naphthol-γ-sulphonic acid, from Dahl's acid.

The first of these acids has recently received a novel application as a photographic developer under the name of *eikonogen* (R. Meldola, *Jour. Soc. Chem. Ind.*, viii. 958). It may be obtained by the reduction of the azo-dye known as "Croceïn orange," "Brilliant orange" or "Ponceau 4GB" (Part I. page 184), obtained by the reaction of Schäffer's β-naphthol-sulphonic acid (Part I. page 194) on diazobenzene chloride. It may be obtained from its nitroso-derivative by dissolving the ammonium or other salt of Schäffer's acid in ice-cold water, together with an equivalent quantity of sodium nitrite, and then gradually adding hydrochloric acid to acid reaction, when the nitroso-acid is at once formed, and imparts an orange colour to the solution. The acid can be purified by conversion into a barium or calcium salt (*Jour. Chem. Soc.*, xxxix. 44), or the solution may be at once reduced to the amido-acid by treatment with zinc-dust or stannous chloride.

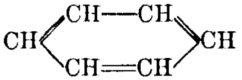
Two other amido-β-naphthol-monosulphonic acids are obtainable by heating with caustic alkali, to 200°–280°, the two β-naphthylamine-disulphonic acids respectively obtained by treating with the two isomeric β-naphthol-disulphonic acids R and Y (described in *Eng. Patent*, 1878, No. 1715). They differ from the amidonaphthol-sulphonic acids, referred to above, in yielding diazo-compounds. They can also be combined with various tetrazo-compounds, giving blackish violet or blue-black dye-stuffs. The following table shows some of their reactions (*Eng. Patent*, 1889, No. 15176). *R salt* is the sodium salt of β-naphthol-disulphonic acid :—

	R.	Y.
Solution of neutral salts in water.	Violet fluorescence.	Blue.
Reaction with ferric chloride.	Dark blue coloration, turning to dun colour.	Dirty claret-red coloration.
Reaction with bleaching-powder solution.	Light yellowish-brown coloration, which disappears rapidly on adding excess of the reagent.	Dark reddish-brown coloration, which disappears gradually on adding excess of the reagent.
Diazo-compound.	Reddish orange.	Canary yellow.
Combination of the diazo-compound with "R salt" in an alkaline solution.	Claret red.	Violet-black.

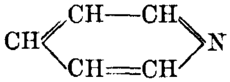
PYRIDINE BASES. $C_nH_{2n-5}N$.

These bases, metameric with aniline and its homologues, are contained in coal-tar naphtha; in shale-oil; in peat-tar; in tobacco-smoke; and, together with ammonia and methylamine and its homologues, in the product called "Dippel's oil," obtained by the distillation of bones and other animal matters. Pyridine itself has received several technological applications, and is of great interest theoretically in relation to the alkaloids.

Pyridine may be regarded as benzene, in which one of the CH groups has been replaced by N.[1] Thus:—



Benzene.



Pyridine.

The homologous bases are derived from pyridine by the substitution of CH_3, C_2H_5, &c., for one or more of the hydrogen atoms, and consequently admit of isomeric modification according to the position of the substituted atoms in the chain.

The following is a list of the bases of the pyridine series. The

[1] The relationship between various organic bodies (hypothetical and otherwise), of which the names commence with the root *pyr* is shown by the following formulæ (compare page 30). The hydrocarbon *pyrene* has the constitution of a phenylene-naphthalene, and is not related closely to the bodies tabulated below:—

Piazine.	*Pyridine.*	*Pyrrol.*	*Pyrazole.*
$N\left\{\begin{array}{l}:CH.CH:\\ .CH:CH.\end{array}\right\}N$	$N\left\{\begin{array}{l}:CH.CH:\\ .CH:CH.\end{array}\right\}CH$	$HN\left\{\begin{array}{l}.CH:CH.\\ .CH:CH.\end{array}\right\}$	$HN\left\{\begin{array}{l}.N:CH.\\ .CH:CH.\end{array}\right\}$
Piazine Dihydride.	*Pyridine Dihydride.*	*Pyrroline.*	*Pyrazoline.*
$N\left\{\begin{array}{l}:CH\ .CH:\\ .CH_2.CH_2.\end{array}\right\}N$	$N\left\{\begin{array}{l}:CH\ .CH:\\ .CH_2.CH_2.\end{array}\right\}CH$	$HN\left\{\begin{array}{l}.CH\ :CH_2.\\ .CH_2.CH_2.\end{array}\right\}$	$HN\left\{\begin{array}{l}.N:CH.\\ .CH_2.CH_2.\end{array}\right\}$
Piazine Hexahydride (Diethylene-diamine).	*Pyridine Hexahydride* (Piperidine).	*Pyrrolidine.*	*Pyrazine.*
$HN\left\{\begin{array}{l}.CH_2.CH_2.\\ .CH_2.CH_2.\end{array}\right\}NH$	$HN\left\{\begin{array}{l}.CH_2.CH_2.\\ .CH_2.CH_2.\end{array}\right\}CH_2$	$HN\left\{\begin{array}{l}.CH_2.CH_2.\\ .CH_2.CH_2.\end{array}\right\}$	$HN\left\{\begin{array}{l}.NH\ .CH_2.\\ .CH_2.CH_2:\end{array}\right\}$
Quinone.	*Pyrone.*	*Pyridone.*	*Pyrazolone.*
$CO\left\{\begin{array}{l}.CH:CH.\\ .CH:CH.\end{array}\right\}CO$	$O\left\{\begin{array}{l}.CH:CH.\\ .CH:CH.\end{array}\right\}CO$	$HN\left\{\begin{array}{l}.CH:CH.\\ .CH:CH.\end{array}\right\}CO$	$HN\left\{\begin{array}{l}.N:CH.\\ .CO.CH_2.\end{array}\right\}$

Piazine has merely a hypothetical resistance, and the dihydride is known only through its diphenyl-derivative. Pyrone and pyrazine, also, are only known by their derivatives. *Pyrazole*, $C_3H_4N_2$, has been recently obtained by acting on hydrazine hydrate with epichlorhydrin in presence of zinc chloride:—

$$2N_2H_4 + C_3H_5ClO = C_3H_4N_2 + HCl + H_2O + 2NH_3.$$

Pyrazole is a basic substance crystallising in needles, melting at 70°, and boiling at 188°. It is readily soluble in water, alcohol, and ether.

boiling-points and specific gravities are only approximate, as the isomeric modifications exhibit sensible differences in their physical properties.

Formula.	*Base.*	*Boiling-Point.* ° C.	*Specific Gravity* at 0° C.	at 22° C.
C_5H_5N	Pyridine.	115-116	·9858	...
C_6H_7N	Picoline (o-Methyl-Pyridine).	133-135	·9613	·933
C_7H_9N	Lutidine (γ-Ethyl-Pyridine).	154	·9443	...
$C_8H_{10}N$	Collidine.	179	·921	...
$C_9H_{13}N$	Parvoline.	188	·906	...
$C_{10}H_{15}N$	Corridine.	211	...	·974
$C_{11}H_{17}N$	Rubidine.	230	...	1·017
$C_{12}H_{19}N$	Viridine.	251	...	1·024

From the above table it is evident that the boiling-points rise as the number of carbon-atoms in the molecule increases. For the first four members of the series the specific gravity diminishes, with increase in the molecular weight, but with the higher members the reverse is recorded as being the case. The lower members are miscible with water in all proportions, but collidine and its higher homologues are insoluble, or nearly so, in water.

If a drop or two of pyridine, or one of its homologues, be warmed in a test-tube with a similar quantity of methyl iodide, the product mixed with powdered caustic potash and moistened with water, and heat applied, a highly characteristic and peculiar odour is produced, owing to the formation of a pyridic dihydride. It resembles that of a mixture of mustard oil and isonitrile. The least trace of pyridine or its homologues can be detected in this way. A somewhat similar odour is obtained when a quinoline base is treated in the same manner, but the aniline bases and piperidine do not give the reaction. The foregoing test, due to A. W. Hofmann, is modified by de Coninck as follows:—1 c.c. of the base is gradually mixed with 2 c.c. of methyl iodide, the liquid being cooled during the mixing. The crystalline product is dissolved in about 5 c.c. of alcohol, the liquid heated to boiling, and very concentrated caustic potash solution dropped in. A blood-red colour is produced, and the liquid finally becomes dark brown if a pyridine base be present (*Jour. Chem. Soc.*, l. 897). Piperidine, sparteine, cicutine, and the aniline bases give no similar reaction.

The bases of the pyridine series are tertiary monamines, and

form with alkyl iodides compounds[1] which are not decomposed by *caustic potash, but yield caustic hydroxides by reaction with silver* oxide (compare page 18).

The pyridine bases and their salts exert a soporific action on the higher animals. When inhaled, pyridine acts as a respiratory sedative. It has been successfully used as a heat stimulant and as a topical antiseptic in diphtheria. Penzhold found pyridine to act as a general antiseptic, especially as regards *mycelia.* On the lower animals, pyridine and its homologues act as violent poisons, and have been successfully employed in 0·2 per cent. solution for destroying the scab-acarus in sheep, the vine-louse, and other injurious insects. The pyridine bases appear to be little, if at all, inferior to nicotine for these purposes, and have also been employed in disinfecting powders.

Isolation of Pyridine Bases.

For the *preparation* of the pyridine bases, bone-oil, or the fraction of coal-tar or shale-oil boiling between 80° and 250°, should be agitated with sulphuric acid diluted with twice its measure of water, the treatment being repeated to ensure the complete solution of the bases. The acid liquid is separated and distilled (or boiled by a current of steam) till the vapours no longer redden a slip of fir-wood moistened with hydrochloric acid, showing that all the pyrrol has been driven off. The liquid is then filtered through linen to separate tarry matters, an excess of caustic soda added, and the whole distilled with steam as long as bases continue to pass over, as indicated by the production of fumes by contact of the vapours with hydrochloric acid. The distillate is allowed to cool, and is then treated gradually with a large quantity of solid caustic potash or soda, till the pyridine bases separate as an oily layer on the surface of the alkaline ley.[2] The upper stratum is separated, and, if it contains aniline, fuming nitric acid is cautiously added and the mixture gradually heated to boiling, whereby the aniline is destroyed, while the pyridine bases remain intact.[3] Water is then added, the precipitate filtered off, and the filtrate

[1] Their methiodides (PyMeI) strongly excite the brain and paralyse the extremities.

[2] The potash can be greatly economised, with a loss of some of the higher homologues, by rendering the distillate acid with hydrochloric acid, and concentrating it to a small bulk by evaporation at a gentle heat before adding caustic potash.

[3] Greville Williams destroys aniline and its homologues by heating with potassium nitrite and hydrochloric acid. Häusermann converts the aniline into sulphate, which salt is much less soluble than the sulphates of the other bases.

again treated with solid caustic potash. The layer of bases is removed, and further treated with stick potash or soda for several days, or until no more alkali dissolves. It is only by prolonged contact with solid caustic alkali that the bases can be freed from water, and it is absolutely necessary to obtain them in a perfectly anhydrous state before attempting to separate them by fractional distillation. This is a very tedious operation, but is greatly facilitated by operating in a vacuum, and by the employment of a Hempel's tube or Henninger's or Glynsky's bulbs (Vol. I. page 14; Vol. II. 501). Goldschmidt and Constam (*Jour. Soc. Chem. Ind.*, iii. 159) found that the mixture of bases extracted by vitriol from coal-tar boiled between 92° and 200°, and after repeated fractionation a little passed over below 100°, and about one-half between 114° and 117° (pyridine), while above this temperature no constant boiling-point was observed. Very little distilled above 160°. The most volatile fraction boiled constantly at 92°–93°, and was found to be a definite hydrate of pyridine, from which treatment with solid caustic potash caused a separation of absolute pyridine, boiling at 114°–115°.

C. Häusermann has pointed out that the amount of sulphuric acid employed in English tar-works for treating 50 and 90 per cent. benzols is insufficient to remove the bases. He found up to 0·10 per cent. of pyridine in commercial 50 per cent. benzol, and 0·25 per cent. in the toluol made from this. Hence the nearly pure benzene, toluene, xylene, &c., now largely manufactured, can be employed with advantage for the preparation of the pyridine bases, as the tedious fractionation has already been accomplished. Thus the base extracted by diluted sulphuric acid from toluene will be nearly pure pyridine; from xylene, chiefly picoline; and from burning and solvent naphtha, the higher homologues. English-made toluene yields about 0·5 per cent. of pyridine, and a similar amount of picoline can be extracted from commercial xylene. Pyridine is more commonly made from crude heavy naphtha, and picoline from the lighter creosote oils.

Pyridine.

$$C_5H_5N\text{; or } CH\left\{\begin{array}{l}:CH.CH:\\ .CH:CH.\end{array}\right\}N$$

This body is the lowest and most important member of the pyridine series of bases. It has been used as an antiseptic and germicide, and is employed in Germany for "denaturating" alcohol. Pyridine is the starting-point in the preparation of several valuable antipyretics, and many of the natural alkaloids are derivatives of it.

The method of preparing pyridine from tars has already been sufficiently indicated. It may be obtained by several interesting synthetical reactions, as by passing a mixture of acetylene and hydrocyanic acid through a red-hot tube:—$2C_2H_2 + CHN = C_5H_5N$. Pure pyridine is conveniently obtained in small quantity by distilling nicotinic acid with lime:—$C_5H_4N.COOH + CaO = C_5H_5N + CaCO_3$.

Commercial pyridine may be purified[1] by dissolving 200 c.c. in 400 c.c. (or a sufficiency) of strong hydrochloric acid, filtering the liquid if necessary, and then adding 1000 c.c. of a 30 per cent. aqueous solution of potassium ferrocyanide. The precipitate is filtered off and washed with cold water, in which the hydroferrocyanides of ammonia and the picolines are easily soluble, while the corresponding salt of pyridine dissolves but sparingly. The washed precipitate is treated with a cold, highly concentrated solution of caustic soda, when the pyridine separates as an oily layer; and, thus obtained, it contains a considerable but variable proportion of water, but if desired may be rendered anhydrous by treatment with sticks of caustic potash or soda, which should be renewed until they cease to liquefy on standing.

Pure pyridine is a colourless liquid, having a most powerful and persistent odour, and producing a bitter taste in the mouth and at the back of the throat. The vapour causes severe headache. Pyridine has a specific gravity of ·9858 at 0° C.,[2] and boils at 116°·7 according to Anderson, or 115° according to Thenius. The presence of water, which it is difficult to separate completely, and which pyridine absorbs with avidity from the air, greatly reduces the boiling-point. Pyridine seems to form a definite hydrate, $C_5H_5N, 3H_2O$, of specific gravity 1·0219, boiling constantly at 92°–93° C.

Pyridine dissolves in water in all proportions, but is precipitated from its solutions by excess of strong potash or soda. It is also miscible with alcohol, ether, chloroform, benzene, and the fatty oils.

The effects of pyridine on animals are described on page 98.

Pyridine is a powerful base, neutralising acids completely and fuming like ammonia in presence of hydrochloric acid and other volatile acids. It blackens calomel, and precipitates many metallic solutions. Pyridine has no effect on a solution of calcium chloride,

[1] Pyridine might probably be advantageously purified from pyrrol and strong-smelling impurities by dissolving it in petroleum spirit and passing hydrochloric acid gas, the precipitated hydrochloride of pyridine being removed, pressed, and dried at a gentle heat.

[2] According to A. Ladenberg (*Ber.*, xxi. 289), the specific gravity of pyridine prepared from the mercuro-chloride is 1·0033 at 0° C.

but on passing carbon dioxide through the liquid calcium carbonate is precipitated. (No precipitate is produced if aniline be substituted for pyridine in this reaction.) Absolute pyridine has no action on litmus, but in presence of water it turns it strongly blue, though the reaction is not capable of being employed for titrating the base, for which purpose methyl-orange is suitable. On phenolphthaleïn pyridine has no action.

Pyridine is an extremely stable body. It is unaffected by treatment with chromic or fuming nitric acid, and these reagents may be employed to free it from aniline and empyreumatic impurities.

When chlorine is passed into a chloroformic solution of pyridine, an additive-compound, C_5H_5N,Cl_2, separates in white flakes. Bromine forms a similar unstable compound. A substitution-product, dibrompyridine, $C_5H_3Br_2N$, is formed by heating to 200° a mixture of pyridine hydrochloride and bromine, or the orange-coloured precipitate formed on adding bromine to a solution of pyridine hydrochloride. It is precipitated by adding water to its solution in strong hydrochloric acid, in needles melting at 109° but commencing to sublime at 100°. It is soluble in ether and unacted on by alkalies, acids, or oxidising agents.

By reduction with tin and hydrochloric acid, pyridine is converted into piperidine, $C_5H_{11}N$, identical with the substance obtained by hydrolysis of piperine, the alkaloid of pepper.

Dipyridine, $C_{10}H_{10}N_2$, is obtained with other products by heating pyridine with sodium. Dipyridine is a base, which melts at 108°, sublimes at a higher temperature in long needles, and forms a hydrochloride, $C_{10}H_{10}N_2,2HCl$, the solution of which yields with potassium ferrocyanide a blue precipitate which dissolves in hot water to form a purple solution.[1]

Para-dipyridyl, $C_5H_4N.NC_5H_4$, formed simultaneously with dipyridine, is a base, crystallising in long needles melting at 114° and boiling at 305° (*Jour. Chem. Soc.*, xliv. 483). Both these bodies yield iso-nicotinic acid on oxidation, while the isomeric *meta*-dipyridyl yields nicotinic acid.

SALTS OF PYRIDINE.

Pyridine forms well-defined salts, most of which are crystallisable and deliquescent. They are odourless when pure, and can be dried without change at 100°, but become slightly coloured on exposure to air and light.

[1] *Iso-dipyridine*, $C_{10}H_{10}O_2$, as obtained by fractionating the mother-liquors from the preparation of dipyridine, is a yellow oil which does not solidify in a mixture of snow and salt, even on addition of crystals of pyridine. It has a specific gravity of 1·08, and is a strong base, sparingly soluble in water, but miscible in all proportions with alcohol and ether.

Pyridine Nitrate, C_5H_5N,HNO_3, forms slender, colourless needles, or short thick prisms, very easily soluble in water, but less so in alcohol, and insoluble in ether.

Pyridine Sulphate, $(C_5H_5N)_2,H_2SO_4$, is crystalline, and extremely soluble in water and alcohol.[1]

Pyridine Hydrochloride, C_5H_5N,HCl. When pyridine is neutralised with hydrochloric acid, and the solution evaporated at 100°, a syrupy liquid is obtained, which, on cooling, becomes gradually converted into a mass of radiating crystals. The salt deliquesces in moist air, and sublimes unchanged at a high temperature. It is volatile to a very notable extent at 100°, and hence cannot be dried at that temperature without loss. It is readily soluble in water and alcohol, but insoluble in ether.

With platinic chloride, a solution of pyridine hydrochloride yields a yellow crystalline precipitate of the *chloroplatinate*, $(C_5H_5N,HCl)_2PtCl_4$, easily soluble in boiling water, less so in alcohol, and insoluble in ether. When pyridine chloroplatinate, free from excess of platinic chloride, is boiled with water for many hours, it is converted into the hydrochloride of platino-pyridine, $C_{10}H_8PtN_2,4HCl$, with libration of 2HCl. The new substance is a sulphur-yellow, insoluble body, which evolves pyridine when boiled with caustic alkali.

Pyridine Picrate, $C_5H_5N,HC_2H_2(NO_2)_3O$, is deposited in beautiful yellow needles when picric acid in aqueous solution is added to a solution of an equivalent weight of pyridine. The salt has a remarkable tendency to carry picric acid down with it, so that if twice the equivalent proportion of picric acid be employed, the product has the percentage composition of an acid salt, $Py,2\overline{Pc}$; but its real nature is indicated by its behaviour with ether, which dissolves out the free picric acid, leaving the normal picrate. Pyridine picrate may also be prepared by mixing strong solutions of sodium picrate and pyridine hydrochloride. The salt melts at 126°·5 C., and is soluble in 91 parts of cold water, but in less than 6 parts of boiling water. It is readily soluble in hot alcohol, but requires about 100 parts of the cold solvent, and is deposited on cooling in long, slender, interlaced needles of a beautiful yellow colour. It is only very slightly soluble in ether, chloroform, or benzene, and practically insoluble in petroleum spirit, but it dissolves with great facility in pyridine and cresylic acid. It is readily soluble on warming in ether, benzene, or petroleum spirit containing 10 per

[1] In *Watts' Dictionary*, vol. i. page 755, there is only described an acid sulphate, which is said to be obtained by evaporating sulphuric acid with excess of pyridine.

cent. of cresylic acid, and is freely soluble in aqueous solution of pyridine and sodium cresylate (A. H. Allen).

Pyridine picrate has an intensely bitter taste and nauseous pyridic after-taste. A moderate dose, for example, produces violent vomiting. It is a valuable insecticide.

Pyridine is remarkable for its tendency to form compounds with metallic salts. These bodies are more or less liable to decomposition by washing or boiling with water, and lose pyridine when heated to 100°, or a somewhat higher temperature. The zinc chloride compound, $ZnCl_2,2C_5H_5N$, separates as a voluminous white precipitate on treating an aqueous solution of zinc chloride with excess of pyridine. It crystallises from water in long, white silky needles, which, when repeatedly washed, or boiled with water, decompose into pyridine and a basic zinc chloride. The zinc chloride compound dissolves in hydrochloric acid to form a double chloride of zinc and pyridine, $ZnCl_2,(C_5H_5N,HCl)_2$, which forms groups of white lustrous needles. Cadmium chloride behaves with pyridine in a manner similar to zinc chloride, the compound formed, $CdCl_2,2C_5H_5N$, crystallising in needles and being partially decomposed by a large quantity of water. The cupric chloride compound is precipitated in fine greenish silky needles on adding pyridine to an alcoholic solution of cupric chloride. It is soluble in pyridine, in aqueous solutions of pyridine, and in ammonia. With mercuric chloride, a very dilute aqueous solution of pyridine (1–1000) yields a precipitate which dissolves extremely easily in warm water, and separates out, as the solution cools, in long white needles. With mercuric iodide, pyridine forms a compound which crystallises from alcohol in beautiful white needles.

From acid solutions of pyridine, phosphotungstic acid throws down a very difficultly soluble precipitate.

Detection and Determination of Pyridine.

The recognition and determination of pyridine are to a great extent based on the properties and reactions already described. In the free state, the smell and basic character of pyridine amply suffice for its recognition in the absence of other basic substances of powerful odour, and it is readily liberated from its salts by addition of caustic soda, and obtained free from every interfering substance by distilling its aqueous solution. It may also be extracted from its aqueous solution by agitation with ether, provided that the liquid be saturated with caustic soda.

In the absence of ammonia, or other bases, free pyridine may be determined by titration with standard acid and methyl-orange (not

litmus). 1 c.c. of normal acid neutralises 0·079 gramme of pyridine.

From *aniline*, pyridine is distinguished by not giving any coloured product on adding a solution of bleaching powder, though the liquid acquires a new and peculiar odour.

The presence of *ammonia* in pyridine can be recognised (in the absence of fixed alkalies) by the red coloration produced in the aqueous solution by phenol-phthaleïn, on which pure pyridine has no action. If the indicator be used in considerable quantity, and a low temperature employed (as recommended by J. H. Long, *Analyst*, xv. 53), the ammonia can be approximately determined by titrating the aqueous solution with standard acid.

K. E. Schulze recommends ferric chloride as an indicator (see page 106). According to W. Lang, the traces of pyridine sometimes contained in commercial *alcohol* may be detected and removed by shaking the spirit with powdered zinc chloride; or, according to W. Kirschmann, by the addition of an acid solution of aluminium sulphate. In the former case, the pyridine is removed in the form of its zinc chloride compound, and in the latter case pyridine alum is formed.

The traces of pyridine sometimes present in *fusel oil* may be detected by adding picric acid, which occasions a formation of pyridine picrate.

For the detection of traces of pyridine in commercial *ammonia*, H. Ost recommends that the sample should be nearly neutralised, when the odour of pyridine may be recognised. By distilling the nearly neutralised liquid, collecting the distillate in hydrochloric acid, evaporating, and extracting the residue with absolute alcohol, a solution is obtained containing but little ammonium chloride. What is present is removed by boiling off the alcohol and adding platinic chloride solution, when, on evaporating the filtrate and adding alcohol, the pyridine chloroplatinate crystallises in smooth, ramifying, orange-red prisms, readily soluble in boiling, but very sparingly in cold, water.

Commercial Pyridine, as now produced, consists chiefly of pyridine and picoline. Ammonia is apt to be present in notable quantity, as also pyrrol and other strong smelling impurities.[1] A considerable but variable proportion of water is present.

Pyridine is employed in Germany, in conjunction with wood

[1] The pyridine produced at certain works becomes turbid when diluted with more than 40 per cent. of water, whereas the best makes are miscible with water in all proportions. On distilling the former brands the disturbing impurity is left in the "tailings."

spirit and turpentine, for "denaturating" spirit. An article intended to be used for this purpose is required to answer to the following official tests.

1. The colour must not be deeper than straw-yellow. 2. If 1 c.c. of the sample be dissolved in 250 c.c. of distilled water, and 20 c.c. of the resultant solution be treated with a 5 per cent. aqueous solution of cadmium chloride, a distinct turbidity should appear in a few moments.[1] 3. When 100 c.c. of the sample is distilled (in a small metal flask provided at the top with a small globe, which is connected with a Liebig's condenser, a thermometer being fitted to the globe, and a moderate heat applied) so that the distillate passes over in separate drops, 90 per cent. should have distilled when the thermometer stands at 140° C. 4. When the sample is mixed with twice its measure of water it must wholly dissolve, and no oily drops must separate even after long standing. 5. Four drops of the sample heated on platinum foil over a Bunsen burner should burn with a sooty flame, and leave no residue. 6. When 20 c.c. of the sample is shaken with an equal measure of a solution of caustic soda of 1·4 specific gravity, a layer of anhydrous bases, measuring at least 18 c.c. (= 90 per cent.), should separate out on standing.

The last test is now usually replaced by one prescribing the use of solid caustic potash. 50 c.c. measure of the sample is placed in a graduated cylinder, furnished with a stopper, and a long stick of potash immersed in it. The alkali gradually absorbs the water from the pyridine, and forms a lower layer of saturated solution. A second stick is added as soon as the first has sunk much below the surface of the pyridine, and is followed by a third if the second liquefies completely or considerably. Agitation should be avoided, and care must be taken that the last stick is left in contact with the upper layer of bases until the action is at an end. It is then cautiously removed with a bent wire, or broken down by a glass rod, and the volume of the layer of anhydrous bases carefully observed. By this test, commercial pyridine usually shows from 8 to 10 per cent. of water (= 92 to 90 per cent. of anhydrous bases).

Instead of determining the water, K. E. Schulze recommends titration of the bases with standard acid. For this purpose 5 c.c. of the sample should be dissolved in water, and the solution diluted to 100 c.c. To 20 c.c. of this solution (= 1 c.c. of the sample) is added 1 c.c. of a 5 per cent. aqueous solution of ferric chloride.

[1] Wepper and Lüders (*Jour. Soc. Chem. Ind.*, vii. 762) have pointed out the unreliable character of this test, which they attribute to the varying composition of cadmium chloride. Of two samples of the salt, only one gave the reaction with pyridine. They recommend the employment of a stronger solution of the pyridine than that prescribed in the test.

Normal sulphuric acid is then run in slowly with agitation, till the precipitated ferric hydroxide is redissolved. 1 c.c. of normal acid (containing 49 grammes of H_2SO_4 per litre) corresponds to ·079 gramme of pure anhydrous pyridine, or to ·095 gramme of picoline.

Pyridine intended for pharmaceutical or medicinal use should not be altered by light; a 10 per cent. solution in water should not be reddened by phenol-phthaleïn (presence of ammonia); and 5 c.c., to which 2 drops of decinormal permanganate have been added, should retain a red colour for at least an hour.

Piperidine. $C_5H_{11}N = C_5H_5(H_5)NH$.

This body has the constitution of a pyridine hexahydride.[1] It is obtained by the reduction of pyridine by nascent hydrogen. The following formulæ show the relation of pyridine to piperidine and piperazine:[2]—

$$CH\left\{\begin{matrix}:CH.CH:\\ .CH:CH.\end{matrix}\right\}N \qquad CH_2\left\{\begin{matrix}.CH_2.CH_2.\\ .CH_2.CH_2.\end{matrix}\right\}NH \qquad HN\left\{\begin{matrix}.CH_2.CH_2.\\ .CH_2.CH_2.\end{matrix}\right\}NH$$

Pyridine. *Piperidine.* *Piperazine.*

Piperidine is also obtained by rapidly heating pentamethylene-diamine (amylene-diamine) hydrochloride:—

$$C_5H_{10}(NH_2)_2,HCl = C_5H_{11}N + NH_4Cl.$$

Piperidine is also produced by the hydrolysis of piperine, $C_{18}H_{18}NO_3$, the alkaloid of pepper, which, on boiling with alkalies, splits into piperidine and piperic acid:[3]—

$$C_{17}H_{19}NO_3 + H_2O = C_5H_{11}N + C_{12}H_{10}O_4.$$

Piperidine is a colourless limpid liquid, of peculiar odour, resembling at the same time that of pepper and ammonia, and has

[1] Pyridine di-and tetra-hydrides and their homologues are capable of existing theoretically. The latter class, called piperideïns, have been prepared by the action of caustic soda and bromine on the piperidines (*Ber.*, xx. 1645).

[2] PIPERAZINE is probably identical with diethylene-diamine. It is a strong base, melting at 104°–107°, boiling at 135°–138°, and absorbing carbon dioxide from the air. Piperazine has neither caustic nor toxic properties, and passes through the system unchanged, but dissolves uric acid in large amount, forming the neutral urate, $C_4H_{10}N_2,C_5H_4N_4O_3$. *Piperazine phosphate* forms four-sided tabular crystals, which character, and those of the bismutho-iodide, distinguish piperazine from spermine, $C_{10}H_{26}O_4$, which otherwise it closely resembles.

[3] A small quantity of piperidine is said to be obtained on distilling pepper with water alone, probably owing to partial decomposition of the piperine by water or a ferment (W. Johnstone, *Analyst*, xix. 46).

a very caustic taste. It boils and distils unchanged at 106°, and dissolves in all proportions in water and alcohol. When piperidine is treated with water heat is evolved.

Piperidine is a powerful base. Its aqueous solution restores the blue colour of reddened litmus-paper, and behaves like ammonia with metallic solutions, except that the precipitates produced with salts of zinc and copper are not soluble in excess. Piperidine absorbs carbon dioxide from the air, and if the gas be passed into a solution of calcium chloride, to which piperidine has been added, calcium carbonate is precipitated. Piperidine may be estimated by titration with standard acid, using either litmus or methyl-orange as an indicator.

Piperidine forms a series of readily crystallisable salts, most of which are soluble. The *chloroplatinate*, $(C_5H_{11}N)_2H_2PtCl_6$, forms orange needles, very soluble in water, but less so in alcohol.

Piperidine is a secondary amine. When dropped into cooled methyl iodide it forms the compound $C_5H_{10}(CH_3)N,HI$. When distilled with alkali this yields the free base methylpiperidine, which, when heated under pressure with methyl iodide, gives the iodide of dimethyl-piperylene-ammonium, $C_5H_{10}(CH_3)_2NI$.

The homologues of piperidine are called by Ladenburg pipecolines, $C_5H_{10}(CH_3)N$, lupetidines, $C_5H_9(CH_3)_2N$, copellidines, $C_5H_8(CH_3)_3N$, &c.

Piperidine is closely related to a number of the natural alkaloids besides piperine, as will be seen from the following formulæ :—

CONINE. Dextro-α-normal-propyl-piperidine.	$CH_2\left\{\begin{matrix}CH_2.CH(C_3H_7)\\CH_2.CH_2\end{matrix}\right\}NH$
CONHYDRINE. Probably hydroxy-conine.	$CH_2\left\{\begin{matrix}CH_2.CH(OH)\\CH_2.CH_2\end{matrix}\right\}N(C_3H_7)$
TROPINE. Methyl-α-hydroxyethyl-tetrahydropyridine.	$CH_2\left\{\begin{matrix}CH_2.CH(C_2H_4OH)\\CH{:}CH\end{matrix}\right\}N(CH_3)$
NICOTINE. Hexahydro-dipyridyl.	$C_5H_4(H_8)N.N(H_3)C_5H_4$

Homologues of Pyridine.

The homologues of pyridine occur with that base in the products of the distillation of bones, coal, &c. Various members of the class have been obtained synthetically.

PICOLINES. METHYL-PYRIDINES. C_6H_7N; or $C_5H_4(CH_3)N$.

Three isomeric modifications of picoline exist, differing according to the orientation of the CH_3 group in relation to the N. The pico-

line of coal-tar is chiefly the ortho-modification (1 : 2), often called α-picoline, mixed with some meta- or β-picoline (1 : 3).[1] Although the former boils at 134° (Weidel; 129°–130°, Lange), and the latter at 140°, they cannot be separated by fractional distillation, but may be isolated by taking advantage of the different solubilities of their chloroplatinates (*Ber.*, xii. 2008). Lange (*Ber.*, xviii. 3436) thinks that α-picoline is preferably separated from bone-oil by means of its sparingly soluble mercuro-chloride. Its specific gravity at 0°, compared with water at 4°, is stated to be 0·9656. The platinochloride melts at 178°, the mercuro-chloride at 167°, and the picrate at 165°. The two last salts are moderately soluble in water. γ-picoline (1 : 4) is produced by the distillation of acroleïn-ammonia, or by heating allyl tribromide with ammonia, and by the reaction of pyridine on methyl iodide. Its presence has been recognised in coal-tar. γ-picoline is stated by A. Ladenburg (*Ber.*, xxi. 285) to boil at 142°·5–144°·5, the specific gravity being 0·9742 at 0° C. The platinochloride melts with decomposition at 231°; the aurochloride at 205°; the mercuro-chloride at 128°–129°; and the picrate at 167°. These characters are not strictly in accordance with the observations of Lange (*Ber.*, xviii. 3436).

The picolines are metameric with aniline, $C_6H_5.NH_2$, which, however, is a primary amine, whereas the picolines have the characters of tertiary bases. In their odour, solubility, basic properties, and characters of their salts, the picolines closely resemble their lower homologue pyridine, but have a lower density and higher boiling-point than the latter body.

LUTIDINES. C_7H_9N.

The bases of this formula may have the constitution of ethyl-pyridines, $C_5H_4(C_2H_5)N$, or of dimethyl-pyridines, $C_5H_3(CH_3)_2N$.

1 : 4 or γ-ethyl-pyridine constitutes the greater part of coal-tar lutidine. It is a colourless liquid of ·9443 specific gravity at 0°, boiling at 154°, and miscible with cold water in all proportions. By oxidation it yields iso-nicotinic acid.

[1] A. Ladenburg (*Ber.*, xxiii. 2688) affirms the existence of two β-picolines; the variety from glycerol boiling at 141°·5–142° (uncorrected), and that from strychnine at 146°–149° (uncorrected). C. Stoehr (*Ber.*, xxiii. 3151) disputes Ladenburg's conclusions, and states that the product obtained by the distillation of brucine or strychnine is not homogeneous. After purification it yields β-methyl-pyridine boiling at 142°–143°, identical with the synthetical product obtained by heating glycerol with acetamide and phosphoric anhydride, which also contains pyridine and β-ethyl-pyridine. The mercuro-chloride melts at 145°–146°, and the chloroplatinate at 201°–202°.

A β-ethyl-pyridine is formed, together with its lower homologues, by heating glycerol with acetamide and phosphoric anhydride (C. Stoehr, *Jour. Prac. Chem.*, [3], xliii. 153). It boils at 140°–145°, has a specific gravity at $^0/_4$ of ·9751, is almost insoluble in water, and yields nicotinic acid on oxidation.

Three isomeric dimethyl-pyridines have been found by Rosenberg in vitriol-tar. Of these, the 1 : 2 : 6 (α–α′) isomeride is a colourless oil boiling at 142°–143°, and having a penetrating odour resembling that of oil of peppermint. It is freely soluble in cold, but less so in hot water. The 1 : 2 : 4 (α–γ) isomer boils at 157°. The 1 : 2 : 3 (α–β) modification has not been isolated, but its presence is inferred from its product of oxidation, isocinchomeronic acid.

Hautsch (*Annalen*, ccxv. 1) has described a lutidine ($C_5H_3(CH_3)_2N$) boiling at 154°, obtained by distilling a mixture of lutidine-tricarboxylate with lime. A lutidine, apparently having the constitution ββ-dimethyl-pyridine, has been prepared by Dürkopf and Göttsch (*Ber.*, xxiii. 1113) by eliminating CO_2 from a dimethyl-pyridine-carboxylic acid obtained by the oxidation of a parvoline boiling at 216°–217°. It boils at 169°–170°, has a feeble, not unpleasant odour, and dissolves sparingly in cold, but readily in boiling water. The specific gravity at $^0/_4$ is 0·9614. The mercuro-chloride crystallises in long sparingly soluble needles, melting at 170°. On oxidation it yields a pyridine-dicarboxylic acid melting at 314°–315°, from which fact, and its external characters, the authors infer it to be dinicotinic acid.

COLLIDINES. $C_8H_{11}N$.

A. Hautsch (*Annalen*, ccxv. 1; *Jour. Chem. Soc.*, xliv. 82) gives the following description of the two known modifications of collidine :—

	α-Collidine. Methyl-ethyl-pyridine. $C_5H_3(CH_2)(C_2H_5)N$.	β-Collidine. β-trimethyl-pyridine. $C_5H_2(CH_3)_3N$.
Boiling-point, ...	178°	171°
Specific gravity at 15°, . .	·853	·917
Solubility in water, . . .	Very slight.	More readily soluble in cold than hot.
Behaviour on exposure to air,	Unchanged.	Becomes brown.
$C_8H_{11}N,HAuCl_4$, ...	Does not melt under water.	Melts under hot water; the dry salt melts at 112°.
Addition of CrO_3 gives . .	Red oil.	Red crystalline precipitate of $(C_8H_{11}N)_2H_2Cr_2O_7$.
Mn, Co, and Fe salts, . .	No precipitate.	Hydroxides gradually precipitated.
$AgNO_3$, ...	No precipitate.	White crystalline precipitate soluble in hot water.

O. de Coninck has described a β-collidine boiling at 195°–196° (*Compt. Rend.*, xci. 296; xcv. 298), having a specific gravity of ·9656 at 0°; and another modification, stated to be a trimethyl-pyridine, has been isolated by J. Mohler (*Ber.*, xxi. 1006; *Jour. Chem. Soc.*, liv. 727) by subjecting the bases from coal-tar to fractional precipitation with potassium ferrocyanide. It is a colourless liquid, unchanged by exposure to air, soluble slowly but to a considerable extent in cold water, and separating again almost completely on warming. The *hydrochloride* forms slender non-deliquescent needles, which sublime, without melting, with partial decomposition. The *sulphate* forms transparent prisms melting at 203°, and the *picrate* long, silky needles melting at 155°–156°.

Pyridine-Carboxylic Acids.

Pyridine itself is an extremely stable body, resisting the strongest oxidising agents; but its homologues yield by oxidation a series of acids in which the alkyl-groups are replaced by a corresponding number of carboxyl-groups. The pyridine-carboxylic acids derive their chief interest from the light they throw on the relationship of the natural vegetable alkaloids to the pyridine bases. Three isomeric pyridine-monocarboxylic acids, $C_5H_4N.COOH$, are obtainable, exactly corresponding to the three isomeric modifications of picoline (methyl-pyridine).[1] The same acids may also be obtained by the action of heat on the di- or tri-carboxylic acids, just as benzoic acid, $C_6H_5.COOH$, is obtained by the action of heat (and lime) on phthalic acid, $C_6H_4.(COOH)_2$. One of them (nicotinic acid) is also obtained by the action of heat on nicotine.

PYRIDINE-MONOCARBOXYLIC ACIDS, $C_5H_4N.COOH$,[2] unite in themselves the basic characters of pyridine with those of an acid. Thus they combine with hydrochloric acid, and the resulting com-

[1] The pyridine-monocarboxylic acids have the empirical formula $C_6H_5NO_2$, and the same percentage composition as nitrobenzene.

[2] The bases from coal-tar boiling between 130° and 140° are boiled in an apparatus furnished with a reflux condenser with ten times their weight of potassium permanganate in 2½ per cent. aqueous solution, until the permanganate is reduced. The oxide of manganese is then filtered off, and the clear liquid concentrated to a small bulk. It is then neutralised and treated with acetate of copper. The precipitate is separated, decomposed by sulphuretted hydrogen, and the filtrate decolorised by animal charcoal. On further concentration and cooling it deposits colourless needles of picolinic acid. The filtrate from the copper precipitate is further evaporated, acidulated with acetic acid, and treated at its boiling-point with acetate of copper. The resulting bluish-green precipitate is separated, boiled rapidly with water, and decomposed by sulphuretted hydrogen. On evaporation, the filtrate deposits colourless crusts of isonicotinic acid.

pound forms double salts with mercuric chloride, platinic chloride, &c.; while, on the other hand, they form a series of well-defined crystallisable salts. The following table exhibits their more important characters:—

	Ortho-Compound or *α-Acid.* *Picolinic Acid.*	*Meta-Compound* or *β-Acid.* *Nicotinic Acid.*	*Para-Compound* or *γ-Acid.* *Isonicotinic Acid.*
Mode of formation, .	Oxidation of α-picoline by permanganate.	Oxidation of β-picoline by permanganate, or nicotine by permanganate chromic acid or nitric acid.	Action of heat on pyridine di- or tri-carboxylic acid. Oxidation of γ-picoline.
Crystalline character, .	Prismatic needles.	Needles.	Needles.
Melting-point, . .	135°; sublimes in lustrous needles.	231.	305°; sublimes in tabular crystals.
Solubility, . . .	Easily soluble in cold or hot water and in alcohol. Nearly insoluble in ether, chloroform, benzene, &c.	Sparingly soluble in cold, easily in warm water; sparingly in ether or chloroform.	Sparingly soluble in water; very sparingly in ether and benzene.
Reaction with neutral lead acetate,	No change.	No change.	...
Reaction with ammoniacal lead acetate,	No change.	White crystalline precipitate.	...
Reaction with cupric acetate,	Slowly deposits shining laminæ and needles of violet-blue colour, and metallic lustre. Soluble in hot water.	Pale blue-green precipitate, insoluble in a large quantity of water.	Green precipitate on warming.
Reaction with ferrous sulphate,	Pale reddish-yellow coloration.	No change.	No change.
Characters of hydrochloride— $C_6H_5NO_2,HCl$,	Large, lustrous, ortho-rhombic prisms, which become rapidly turbid on exposure to air.	Monoclinic prisms, quite permanent in the air.	Large shining crystals.

On heating with lime, the above acids yield pyridine, just as benzoic acid yields benzene under similar conditions. The sodium salts of the α and β acids, when treated in solution with sodium amalgam, give off ammonia, and yield the salt of an unsaturated acid of the fatty series, $C_6H_8O_3$.

PYRIDINE-DICARBOXYLIC ACIDS. $C_5H_3(COOH)_2$. Of the six possible acids of this formula, all are known. They are produced by the oxidation of homologues of pyridine containing two

substituted hydrogen atoms, and also by the oxidation of other substances.

Quinolinic Acid [the α–β modification] is obtained by the oxidation of coal-tar quinoline by permanganate, and is the anologue of phthalic acid, obtained similarly by the oxidation of naphthalene. It crystallises in short prisms, slightly soluble in cold water, more readily in hot water and alcohol, insoluble in benzene. It blackens when heated, and melts at about 223°, apparently being converted into nicotinic acid (*Jour. Chem. Soc.*, xliv. 90). The acid is removed from its aqueous solution by ether.

Lutidinic Acid [α–γ] is similarly produced by the action of permanganate on cinchonine-quinoline. It melts at 235°, is sparingly soluble in cold water, and gives with cupric acetate a pale blue precipitate.

Dipicolinic Acid [α–α'] melts at 226°; *Isocinchomeronic Acid* [α–β] at 236°; and *Dinicotinic Acid* [β–β'] above 285°.

Cinchomeronic Acid [β–γ] is the chief product of the oxidation of quinine by nitric acid, and is also obtained, together with other products, by the similar treatment of cinchonine. It crystallises in white prismatic needles, which melt at 266°–268°, with partial decomposition, and is only very sparingly soluble, even in boiling water. It forms two classes of salts. Its most characteristic reaction is its behaviour with cupric acetate, which does not give a precipitate in the cold, but on heating the liquid becomes turbid, clearing again on cooling. On prolonged boiling, a permanent azure-blue precipitate is formed.

All the dicarboxylic acids which contain a carboxyl-group in the α-position give a reddish-yellow coloration with ferrous sulphate.

PYRIDINE-TRICARBOXYLIC ACIDS, $C_5H_2(CO.OH)_3$, are obtained by the oxidation of certain alkaloids. Thus quinine, quinidine, and cinchonidine, by boiling with an alkaline solution of permanganate, yield *hydroxycinchomeronic acid*, which forms orthorhombic prisms melting (with blackening) at 244°; while berberine, when oxidised by nitric acid, yields the isomeric body *berberonic acid*, crystallising in the triclinic system. Both acids give a deep red colour with ferrous sulphate, destroyed by a mineral acid.

PYRIDINE-PENTACARBOXYLIC ACID, $C_5N(COOH)_5$, forms crystals containing 2 *aqua*. It becomes anhydrous at 120°, and decomposes without melting at 220°. It is freely soluble in water, and is a strong acid, resembling oxalic acid in its power of forming acid and double salts (Hautsch, *Jour. Chem. Soc.*, xliv. 85).

Pyrrol.[1] C_4H_5N, or $C_4H_4.NH$.

This associate of the pyridine bases[2] is a colourless liquid of pungent taste, and odour like that of chloroform. The specific gravity is 1·077, and boiling-point 130°–133°. It is but little soluble in water, and insoluble in alkalies, but dissolves in dilute acids, alcohol, and ether. It is indifferent to most reagents, but appears to possess feebly-marked basic properties. The only definite salt is the picrate, which forms unstable red needles melting at 71°.

Pyrrol turns brown in the air, and when warmed with acids forms a red substance known as pyrrol-red, the reaction apparently occurring being :—$3C_4H_5N + H_2O = C_{12}H_{14}N_2O + NH_3$. A piece of pine-wood, moistened with hydrochloric acid and exposed to the vapour of pyrrol, becomes deep red.

When a cold aqueous solution of isatin is treated with pyrrol and a little dilute sulphuric acid, a heavy blue precipitate, resembling indigo, is obtained. When both reagents are dissolved in glacial acetic acid and boiled, a deep blue solution is obtained, apparently containing the same colouring-matter.

If a solution of phenanthrene-quinone in acetic acid be treated with pyrrol and a little dilute sulphuric acid, a brown precipitate is formed, which dissolves in chloroform with a beautiful violet-red colour. When an aqueous solution of benzo-quinone is treated with pyrrol and dilute sulphuric acid, a dark green precipitate is formed, insoluble in ether. These reactions indicate the close relationship between pyrrol and thiophene, which itself has the constitution of a thio-furfuran. Many of the reactions of pyrrol are also produced by carbazol, which is an imido-diphenyl. Indole has a constitution between pyrrol and carbazol. Thus :—

Pyrrol, C_4H_5N.	*Indole*, C_8H_7N.	*Carbazol*, $C_{12}H_9N$.
$\left\{\begin{array}{l}.CH:CH.\\.CH:CH.\end{array}\right\}NH$	$\left\{\begin{array}{l}.CH:CH.\\.C_6H_4.\end{array}\right\}NH$	$\left\{\begin{array}{l}.C_6H_4.\\.C_6H_4.\end{array}\right\}NH$
Furfuran, C_4H_4O.		*Diphenylene Oxide*.
$\left\{\begin{array}{l}.CH:CH.\\.CH:CH.\end{array}\right\}O$		$\left\{\begin{array}{l}.C_6H_4.\\.C_6H_4.\end{array}\right\}O$
Thiophene, C_4H_4S.	*Thionaphthene*, C_8H_6S.	
$\left\{\begin{array}{l}.CH:CH.\\.CH:CH.\end{array}\right\}S$	$\left\{\begin{array}{l}.CH:CH.\\.C_6H_4.\end{array}\right\}S$	

[1] Pyrrol has been obtained synthetically by passing acetylene and ammonia through a red-hot tube, and also by the dry distillation of the ammonium salts of mucic and saccharic acids.

[2] The proportion of pyrrol contained in coal-tar is very small. It is best prepared by shaking bone-oil with dilute sulphuric acid and fractionating the insoluble portion. The fraction boiling between 100° and 150° is heated

Two isomeric *methyl-pyrrols* exist in bone-oil,[1] besides a *dimethyl-pyrrol*, boiling at 165°, which has also been obtained synthetically, and closely resembles pyrrol. In the homologues of pyrrol occurring in bone-oil, substitution has always occurred in the C_4H_4 group, but by the action of alkyl iodides on potassium-pyrrol substitution of the hydrogen of the NH group can be effected.

TETRAIODO-PYRROL, C_4I_4NH, has been recently introduced into medicine under the name of "iodol." It is prepared by the action of iodised potassium iodide on pyrrol, and forms a tasteless, pale yellow, crystalline powder, having a faint thymol-like odour. It is unchanged at 100°, but gives off iodine vapour at a somewhat higher temperature. Iodol is nearly insoluble in water, but readily in ether and chloroform. It dissolves in three parts of alcohol, and the solution is precipitated by adding water, but not by glycerin. Iodol contains 90 per cent. of iodine and possesses antiseptic and local anæsthetic properties analogous to those of iodoform, over which its slight odour and freedom from toxic properties give it the preference. Iodol can be recognised by the green colour of its solution in sulphuric acid, and by the bright red colour produced when an alcoholic solution is warmed with nitric acid.

QUINOLINE AND ITS ALLIES.

The interesting base which gives its name to the quinoline series bears the same relation to naphthalene that pyridine bears to benzene; that is, it is derived by the substitution of an atom of nitrogen for one of the CH groups of naphthalene (see foot-note, Vol. II. page 507):—

Benzene,	C_6H_6	Pyridine,	C_5H_5N
Naphthalene,	$C_{10}H_8$	Quinoline,	C_9H_7N

with a large excess of solid caustic potash in a reflux apparatus until the whole is fused, when any unchanged oil is separated and the crystalline mass of potassium pyrrol, C_4H_4KN, is powdered, and after being washed with ether is treated with water and distilled with steam, when the pyrrol is regenerated.

[1] To isolate these methyl-pyrrols, the fraction of bone-oil boiling between 140° and 150° is converted into the potassium derivative, and this is heated to 200° in a stream of carbon dioxide. Two isomeric homopyrrol-carboxylic acids are formed. The α-acid melts at 169°·5, and forms a lead salt very soluble in water, while the β-acid melts at 142°·4, and forms a nearly insoluble lead salt. On distilling the respective acids with lime, the corresponding α- and β-homopyrrols are regenerated. The first boils at 148° and the latter at 143° at 743 mm. pressure.

Quinoline may be represented by the following constitutional formulæ. Where substitution occurs in the pyridine-nucleus, α, β, and γ (or P-1, -2, and -3) products are obtained, while substitution in the benzene-nucleus yields *ortho-*, *meta-*, *para-*, and *ana-* derivatives (or B-1, -2, -3, -4), according to the position of the substituted hydrogen atom.

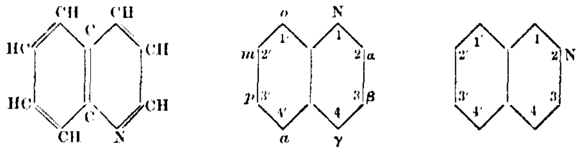


Fig. 1. Fig. 2. Fig. 3.

Just as two isomeric naphthols exist, so two isomeric quinolines are theoretically possible, and appear to have been obtained. Thus the quinoline obtained by distilling quinine, cinchonine, and other alkaloids with potash (fig. 2) appears to differ in some of its reactions from the quinoline contained in coal-tar, which is often called leucoline (fig. 3). On the other hand, Hoogewerff and Van Dorp (*Jour. Chem. Soc.*, xliv. 89) contend that the quinolines obtained from both sources are identical.

A whole series of higher homologues are produced, together with quinoline, on distilling alkaloids with caustic potash.[1] *γ-methyl quinoline* or *lepidine*, $C_9H_6(CH_3)N$, the first member of the series, boils at 266°. Of the next member, *despoline*, $C_{11}H_{11}N$, and the still higher homologues, very little is known.

A parallel series of bases have been found in coal-tar and shale-oils. They are obtained from the fractions of the bases boiling above 200°, and hence distil after the pyridine bases have passed over. *Quinaldine*, or α-methyl-quinoline, $C_9H_6(CH_3)N$, boils at 239°, and sometimes forms 25 per cent. of coal-tar quinoline. It is a colourless liquid (also obtainable synthetically), the oxidation of which yields either a benzene or a quinoline derivative, according to the nature of the oxidising agent.[2] *Iridoline*, isomeric with quinaldine, and probably identical with lepidine, is also con-

[1] If the distillation be conducted in presence of copper oxide, the quinoline obtained is almost free from higher homologues.

[2] When quinaldine is heated with amyl iodide it forms the compound $C_9H_6(CH_3)(C_5H_{11})NI$, which on heating with caustic potash is converted into a cyanine, $C_{28}H_{25}NI$ (page 118). A similar body is obtainable from lepidine, and a mixture of the two has been used for dyeing silk, but the colour is very fugitive. When heated with phthalic anhydride, quinaldine reacts to form a body of the phthaleïn class known as *quinoline-yellow* (see Vol. III. Part I. page 174).

tained in coal-tar. It boils between 252° and 257°, and yields a crystallisable nitrate, chromate, and hydrochloride.

From the acid tar produced in the purification of shale-oil, Robinson and Goodwin (*Trans. Roy. Soc. Edin.*, xxviii. 561; xxix. 265) obtained the following bases of the quinoline series.

Base.	*Formula.*	*Boiling-Point,* ° C.
Tetracoline, . . .	$C_{12}H_{13}N$	290-295
Pentacoline, . . .	$C_{13}H_{15}N$	305-310
Hexacoline, ...	$C_{14}H_{17}N$	325-330
Heptacoline, . . .	$C_{15}H_{19}N$	345-350
Octacoline, ...	$C_{16}H_{21}N$	360-365

Quinoline. Chinoline. C_9H_7N.

This base is formed by distilling quinine, cinchonine, or strychnine with aqueous potash, and by other interesting reactions; but is best prepared by shaking together nitrobenzene (48 parts), aniline (76 parts), glycerin (240 parts), and sulphuric acid (200 parts). When the aniline sulphate has dissolved, a reflux condenser is fitted to the flask, which is heated to 130° till reaction sets in, when the flame is removed. In about three hours, or when action is at an end, the product is cautiously diluted with water, and boiled to get rid of traces of nitrobenzene, after which lime or caustic soda is added, and the quinoline and unchanged aniline distilled over in a current of steam. The oil obtained is separated from the aqueous layer, dehydrated over caustic potash, and fractionally distilled, whereby a separation of the bases is effected tolerably readily, aniline boiling at 184°, and quinoline at 239°. To purify the latter it is again fractionally distilled, and boiled with weak chromic acid mixture (to oxidise any aniline); or the quinoline is dissolved in six parts of water, and strong sulphuric acid added in the exact quantity necessary to combine with the base. After cooling, the liquid is filtered, and the insoluble acid sulphate washed with alcohol till snow-white, and then decomposed by potash.[1]

[1] The reaction in the foregoing reaction may be written thus:—

$$2C_6H_7N + C_6H_5NO_2 + 3C_3H_8O_3 = 3C_9H_7N + NH_2O.$$

The change is undoubtedly due to the formation of acroleïn, C_3H_4O, from the glycerin, and the reaction of this with aniline to form acroleïn-aniline, with simultaneous oxidation by the nitrobenzene:—

$$C_3H_8O_3 + C_6H_5NH_2 + O = C_9H_7N + 4H_2O.$$

The homologues of quinoline may be obtained in an analogous manner, and by

Quinoline is a colourless mobile liquid, having a penetrating and peculiar taste, and an after-taste slightly resembling peppermint-oil. It has a faint aromatic odour, like that of bitter-almond oil. Quinoline evaporates completely but slowly at the ordinary temperature, so that the grease-spot formed by it on paper is not permanent. It boils at 238°–239°, according to most observers; 231°·5, according to S p a l e h o l t z; and 241°·3, according to K r e t s c h y. Its specific gravity is stated to be 1·081 at 0° C., and 1·094 at 20° C., compared with water at the same temperature.

Quinoline is very sparingly soluble in cold water, but more freely so in hot. It is miscible in all proportions with alcohol, ether, carbon disulphide, and fixed and volatile oils; and is also easily soluble in chloroform, amylic alcohol, benzene and petroleum spirit.

On exposure to air, quinoline becomes resinified.

Quinoline has well-marked basic characters, and forms an extensive series of salts, most of which are crystallisable and deliquescent. It precipitates ferric and aluminium solutions, and at a high temperature decomposes ammonium salts.

Quinoline can be titrated fairly accurately with standard acid, if methyl-orange be employed as an indicator.

Reactions of Quinoline and its Salts.

Quinoline salts in aqueous solution are precipitated milky white by caustic alkalies and ammonia, the precipitate being somewhat soluble in excess. From the alkaline liquid, the quinoline can be readily extracted by ether, chloroform, or petroleum spirit.

Iodised iodide of potassium gives a reddish-brown precipitate even in dilute solutions of quinoline salts (1 in 20,000). Potassio-mercuric iodide only precipitates quinoline from tolerably strong solutions (1 in 3000), the precipitate being yellowish white and amorphous, but converted into delicate amber-yellow needles on addition of hydrochloric acid. This reaction is characteristic. Phosphomolybdic acid, in presence of nitric acid, produces a yellowish-white precipitate in quinoline solutions.

Potassium ferrocyanide colours solutions of quinoline salts reddish, and on addition of hydrochloric acid a reddish-yellow amorphous precipitate is thrown down, if the liquid be not too dilute.

Quinoline is precipitated by picric acid, but not by tannic acid or ferric chloride; and its salts, in the solid state, yield no colour-reactions with nitric acid or strong sulphuric acid, either alone or in association with oxidising agents.

With potassium bichromate, if carefully added, quinoline salts

employing derivatives of aniline or its homologues, quinoline substituted in the benzene-ring may be obtained.

yield a precipitate of delicate dendritic crystals of the bichromate $(C_9H_7N)H_2,Cr_2O_7$, said by Donath to be soluble in excess of the reagent. Quinoline bichromate melts at 165° C.

When quinoline is heated with sodium, diquinolyline, $C_9H_6N.C_9H_6N$, analogous to dipyridyl and diphenyl, is formed. When polymerised, quinoline yields yellow needles of diquinoline, $(C_9H_7N)_2$.

When quinoline and amyl iodide are boiled together for a short time, they combine to form a crystalline body containing $C_9H_7(C_5H_{11})NI$. If the product be dissolved in boiling water, and the solution filtered and boiled with caustic soda or ammonia, avoiding excess, a blue colouring matter is formed, which, on allowing the liquid to cool, is precipitated, leaving the solution nearly colourless. The separated substance, called cyanine, is a basic body crystallising in green plates, having a metallic lustre. It is nearly insoluble in cold water, but dissolves in alcohol to form a rich purplish blue solution, which dyes silk blue.

The foregoing reaction, as also that with potassium bichromate, is said not to be obtainable with the quinoline (leucoline) of coal-tar.

Quinoline possesses powerful antiseptic properties. 0·2 per cent. of the tartrate is said to completely prevent the lactic fermentation of milk, the decomposition of urine and gelatin, and the development of bacteria in cultivation-fluid. Even in concentrated solution it does not coagulate albumin, and in the proportion of 1 per cent. it completely destroys the coagulability of the blood. On the other hand, quinoline is remarkably inactive to yeast-cells, and does not affect the alcoholic fermentation, even when present in considerable quantity.

Quinoline has been used in medicine as an antipyretic, the adult dose of the tartrate being from 7 to 12 grains. It is said by some not to produce any unpleasant after-effects, but by others to cause irritation of the stomach and collapse. It is not found in the urine of those who have taken it internally.

Commercial Quinoline is often very impure and quite unfit for medicinal use. C. Ekin (*Pharm. Jour.*, [3], xii. 661) has described a specimen which had a deep brown colour and an odour like oil of bitter almonds. On treating it with hydrochloric acid a large proportion remained insoluble, and was evidently unconverted nitrobenzene, while the soluble part gave the reactions of aniline.

Cinchonine-quinoline often contains *lepidine*. Such samples give the cyanine reaction (see above) with amyl iodide and caustic alkali.

The salts of quinoline should be completely soluble in water,

and the free base in a slight excess of hydrochloric acid. The neutral solution should be free from bitter taste (which indicates the presence of impurity derived from cinchonine), and should not give a coloured precipitate with caustic alkalies.

Quinoline Tartrate, $(C_9H_7N)_3(C_4H_6O_6)_4$, is now used extensively in medicine. It melts at 125° C., and possesses the advantage of being permanent in the air, whereas most of the salts of quinoline are deliquescent. It dissolves in 80 parts of cold water, in about 150 parts of rectified spirit, and in 350 parts of ether. It produces much the same effects as sulphate of quinine, and is given in similar doses, but is far lower in price.

Quinoline Hydrochloride, C_9H_7N,HCl, melts at 94° C., and sublimes unchanged. It dissolves in water, alcohol, and chloroform, and sparingly in cold ether and benzene.

TETRAHYDROQUINOLINE.

$$C_9H_{11}N\ ;\ \text{or}\ C_6H_4\left\{\begin{matrix}CH_2.CH_2\\NH.CH_2\end{matrix}\right\}$$

When quinoline is acted on by nascent hydrogen, it is first converted into dihydroquinoline, C_9H_9N, a solid body melting at 161°, and subsequently into tetrahydroquinoline, which is a liquid boiling at 245°. Both these reduction-products yield nitrosamines, and can be alkylated, and hence are secondary bases. Tetrahydroquinoline possesses stronger antipyretic characters than quinoline itself, and this property is exhibited still more strongly in certain of its derivatives, several of which have received some application in medicine (see below).

Antipyretics allied to Quinoline.

A considerable number of new substances related to quinoline, and mostly allied to tetrahydroquinoline, have been recently introduced as febrifuges and antipyretics. Some of these are very powerful in their action, and appear likely to receive a permanent place in medicine; but they are not periodics, and cannot be substituted for quinine in cases of ague or intermittent fevers. The following are the most important of the antipyretics derived from or related to quinoline.[1]

M-KAIROLINE is the *acid sulphate* of a base having the constitu-

[1] Other antipyretics are described in the sections on anilides, amidophenols, antipyrine, &c. Many interesting facts relating to and relationships of the antipyretics have been collated by T. S. Dymond and an anonymous German author (*Pharm. Jour.*, [3], xvii. 886–895). A fuller and more recent description of them is given in a series of articles on "Modern Materia Medica," contributed by H. Helbing to the *British and Colonial Druggist*, 1891, and since published in a separate form.

tion of methyl-tetrahydro-quinoline, $C_9H_{10}(CH)_3N$, obtained by reducing quinoline by tin and hydrochloric acid, and reacting on the resulting tetrahydroquinoline with methyl iodide.

A-KAIROLINE had a similar constitution, but contained ethyl, C_2H_5, instead of the methyl-group.

M-KAIRINE is the *hydrochloride* of Hydroxy-tetra-hydro-methyl-quinoline,

$$C_6H_3(OH):\left\{\begin{matrix} CH_2.CH_2. \\ N(CH_3).CH_2. \end{matrix}\right\}$$ The corresponding ethyl-derivative is known as *A-Kairine*.

On adding a caustic alkali to the aqueous solution of a kairine, the penetrating characteristic odour and bitter taste of the free base are easily recognised, while the alkaline solution rapidly becomes coloured and deposits a brown humus-like substance. When the aqueous or alcoholic solution of a kairine is treated with an oxidising agent, such as potassium bichromate and an acid, it gives a series of colours ranging from violet-blue to purple, or sometimes greenish. Without the addition of an acid, the solution becomes dark purple, and on standing a violet precipitate is formed, which dissolves in alcohol with black colour. A drop of ferric chloride, added to a dilute and neutral solution of kairine, instantly produces a violet coloration, rapidly changing to brown, with precipitation. An excess of ferric chloride added to a strong solution of kairine produces a nearly black precipitate. Sodium nitrite and dilute sulphuric acid produce an orange or red colour in kairine solutions. Potassium ferrocyanide gives a voluminous precipitate, and phosphotungstic acid a pale yellow precipitate.

The kairines act as powerful antipyretics. Their use is almost obsolete, as their action is somewhat uncertain; and they are said to be liable to produce vomiting, cyanosis, and collapse.

THALLINE is the commercial name of another antipyretic, metameric with *m*-kairine, and having the constitution of a salt of tetrahydro-paraquinanisol:—

$$C_6H_3(O.CH_3):\left\{\begin{matrix} CH_2.CH_2 \\ NH.CH_2 \end{matrix}\right\}$$

Thalline is prepared by heating paramido-anisol and paranitro-anisol with glycerin and sulphuric acid, and reducing the product with nascent hydrogen. Thalline base crystallises in large colourless prisms, having a bitter, saline, and pungent taste. It melts at 42° C., and is sparingly soluble in water, but readily in alcohol, ether, chloroform, or benzene.

Thalline Sulphate, $(C_{10}H_{13}NO)_2H_2SO_4+2H_2O$, is the most common variety of commercial "thalline." It occurs as a yellowish-white, granular or crystalline powder, having a bitter, aromatic taste,

and a faint odour resembling anise and meadow-sweet. It dissolves in seven parts of cold water, but only sparingly in alcohol, and the solutions become darker on exposure to light. A very dilute aqueous solution of commercial thalline gives with ferric chloride a yellow coloration, changing to emerald-green (destroyed by reducing agents), and passing in a few hours to deep red. The reaction is extremely delicate. A green colour is also produced by auric chloride, argentic nitrate, mercuric nitrate, chlorine-water, &c., and, in acid solution, also by solution of bleaching powder and potassium ferricyanide. Strong sulphuric acid dissolves thalline sulphate without coloration, but on addition of nitric acid the liquid becomes deep red, and immediately afterwards yellow-red. Fuming nitric acid colours a dilute aqueous solution reddish. Sulphuric acid and sugar give a red coloration. Iodine colours the solution dark brown, then dingy green. Ammonia forms a white precipitate of the free base, readily taken up by ether on agitation. If not too dilute, solutions of thalline sulphate yield precipitates with the general reagents for alkaloids.

If to an aqueous solution of β-naphthaquinone a small quantity of the solution of a thalline salt be added, and then a drop or two of caustic soda solution, a fine cherry-red coloration is produced, becoming more brilliant on adding nitric acid. The colouring matter is extracted by ether or chloroform.

Thalline Tartrate occurs in commerce as a yellow-white crystalline powder. It dissolves in ten parts of cold water, and the solution gives the same reactions as the sulphate. In alcohol it is very sparingly soluble. The salt contains 52·2 per cent. of thalline.

The salts of thalline become altered by exposure to light.

Thalline salts are powerfully antipyretic, and have been employed in yellow fever. They cause profuse perspiration, and are apt to produce depression, &c. Hence their internal use is practically obsolete. Thalline acts as a direct blood-poison, its antithermic properties being due to the destruction of the red corpuscles. It has found considerable application in the treatment of gonorrhœa. The sulphate is official in the *German Pharmacopœia* of 1890.

Exhibition of thalline causes a dark coloration of the urine. A derivative, which also gives a green colour with ferric chloride, but differs from thalline in being extracted by agitating the acidulated urine with petroleum spirit, should first be removed, and then the unaltered portion of the thalline can be isolated by rendering the urine alkaline with ammonia, and agitating with ether or benzene. Very small quantities of thalline can in this way be recognised in urine.

ETHYL-THALLINE, $C_{10}H_{10}ON(C_2H_5)$, is produced by heating ordinary thalline with ethyl iodide.

THERMIFUGIN is a name given to the sodium salt of methyl-trihydroquinoline-carboxylic acid:—

$$(COONa)C_6H_3 : \left\{ \begin{array}{l} CH_2.CH_2 \\ N(CH_3).CH_2 \end{array} \right\}$$

Quinazolines.

By the replacement of one of the CH groups of quinoline by N, bodies are obtained which bear the same relationship to quinoline that the azines bear to pyridine. Thus:—

Pyridine. $N \left\{ \begin{array}{l} :CH.CH: \\ .CH:CH. \end{array} \right\} CH$	*Quinoline.* $N \left\{ \begin{array}{l} :CH.CH: \\ .C_6H_4. \end{array} \right\} CH$
Ortho-azine (Oiazine). $N \left\{ \begin{array}{l} :N.CH: \\ .CH:CH. \end{array} \right\} CH$	*Ortho-quinazoline* (Phenoiazine). $N \left\{ \begin{array}{l} :N.CH: \\ .C_6H_4. \end{array} \right\} CH$
Meta-azine (Miazine). $N \left\{ \begin{array}{l} :CH.N: \\ .CH:CH. \end{array} \right\} CH$	*Meta-quinazoline* (Phenmiazine). $N \left\{ \begin{array}{l} :CH.N: \\ .C_6H_4. \end{array} \right\} CH$
Para-azine (Piazine). $N \left\{ \begin{array}{l} :CH.CH: \\ .CH:CH. \end{array} \right\} N$	*Para-quinazolin* (Phenpiazine). $N \left\{ \begin{array}{l} :CH.CH: \\ .C_6H_4. \end{array} \right\} N$

A substituted meta-quinazoline having the constitution of a phenyl-dihydrophenmiazine:—

$$N \left\{ \begin{array}{l} :CH.N(C_6H_5). \\ .C_6H_4. \end{array} \right\} CH_2$$

has recently acquired some practical interest as the base of "orexin," a preparation said to have valuable tonic, stomachic, and appetising properties, on which, however, some doubt has been thrown (*Pharm. Jour.*, [3], xx. 709, 825, 977; xxi. 43). The usual dose of orexin is from 2 to 10 grains.

OREXIN, which occurs as a *hydrochloride* having the composition $C_{14}H_{12}N_2,HCl+2H_2O$, is prepared by reacting on the sodium-derivative of formanilide by ortho-nitrobenzyl chloride, according to the equation:—

$$Na(CHO).N.C_6H_5 + Cl.CH_2.C_6H_4.NO_2 = NaCl + CHO.N(C_6H_5).CH_2.C_6H_4.NO_2$$

The nitrobenzyl-formanilide, on reduction with tin and hydrochloric acid, forms the closed chain compound which is the base of orexin:—

$$\left.\begin{matrix}CHO.N(C_6H_5).\\NO_2.C_6H_4.\end{matrix}\right\}CH_23H_2 = 3H_2O + N\left\{\begin{matrix}:CH.N(C_6H_5).\\.C_6H_4.\end{matrix}\right\}H_2$$

Orexin (hydrochloride) crystallises with $2H_2O$ in white needles, melting at 80°. When kept under an exsiccator for some time they become anhydrous, and then melt at 221°. Orexin has a bitter taste, and somewhat intense, burning after-taste. The powder induces violent sneezing. Orexin dissolves readily in water (13 parts) and alcohol, but not in ether. On adding an alkali to the aqueous solution the free base is separated as a white flocculent precipitate readily soluble in ether and chloroform.[1] A solution of orexin yields with mercuric chloride a white precipitate soluble in hot water, and redeposited in white needles on cooling. Potassium bichromate gives a yellow precipitate soluble on heating, and redeposited on cooling in golden yellow needles. Bromine-water is decolorised with formation of a yellowish amorphous precipitate. Orexin reduces potassium permanganate in the cold.

On heating orexin in a test-tube with about twice its measure of zinc-dust, the strong characteristic odour of phenyl-isonitrile is produced. On treating the residue with hydrochloric acid, and adding bleaching-powder solution to the filtered liquid, a blue coloration is obtained, owing to the previous formation of aniline (compare page 45).

ACRIDINE AND ITS ALLIES.

Acridine and its isomer phenanthridine bear the same relation to anthracene and phenanthrene respectively that quinoline bears to naphthalene, and pyridine to benzene (compare page 39). The following formulæ show their constitution and relationship to anthracene and phenanthrene:—

$$C_6H_4:\left\{\begin{matrix}CH\\|\\CH\end{matrix}\right\}:C_6H_4 \qquad \left\{\begin{matrix}.C_6H_4.CH:|\\.C_6H_4.CH:|\end{matrix}\right\}$$

Anthracene. *Phenanthrene.*

$$C_6H_4:\left\{\begin{matrix}CH\\|\\N\end{matrix}\right\}:C_6H_4 \qquad \left\{\begin{matrix}.C_6H_4.CH:\\.C_6H_4.N:\end{matrix}\right\}$$

Acridine. *Phenanthridine.*

Acridine. $C_{13}H_9N$.

Acridine has been prepared synthetically by heating concentrated

[1] The base sometimes separates as an oil, which afterwards crystallises.

formic acid or chloroform with diphenylamine and zinc chloride,[1] and also by various other reactions. Acridine is contained in coal-tar, and may be extracted from the fraction boiling between 300° and 360°, or from crude commercial anthracene, by agitating it with dilute sulphuric acid, precipitating the acid liquid with potassium chromate, purifying the acridine chromate by recrystallisation, precipitating the base by ammonia, and recrystallising it from hot water. The hydrochloride may also be employed for the purification of acridine.

Acridine forms colourless or brownish-yellow rhombic prisms, of very pungent odour and burning taste. It melts at 107°, sublimes in broad needles at about the same temperature, boils unchanged at 360°, and distils with the vapour of water.

Acridine is very slightly soluble in cold, but more readily in boiling water, crystallising on cooling in long needles. It is readily soluble in alcohol, ether, benzene, carbon disulphide, &c.

Dilute solutions of acridine (and its salts) exhibit a strong blue fluorescence, which is green in more concentrated solutions, and disappears if they are very strong.

Certain reactions of acridine solutions with reagents are described on page 126.

The most characteristic property of acridine is its intensely irritating effect on the skin and mucous membrane. Violent sneezing and coughing are produced by inhaling the smallest particle of the dust or vapour. The base and its salts attack the tongue even in minute quantities, and even very dilute solutions cause acute stinging when applied to the tongue or skin.

Acridine has been employed as an insecticide, and compositions containing it have been patented for coating the bottoms of vessels. It is highly probable that the preservative properties of coal-tar creosote oil are partially due to the presence of acridine.

Acridine is a very stable substance. Sulphuric acid has no action upon it, except at a very high temperature, and caustic potash does not react below 280°. Concentrated nitric acid converts acridine into nitro-derivatives. Most other oxidising agents act with difficulty or not at all on acridine, but by the action

[1] Acridine is best obtained by heating a mixture of one part each of chloroform, diphenylamine, and zinc or (preferably) aluminium chloride, with one-half part of zinc oxide, for seven or eight hours, under pressure, to 200°–210° C. The product is boiled with concentrated hydrochloric acid, the filtered liquid poured into water, the liquid again filtered, the acridine precipitated from the solution by ammonia, and recrystallised from hot water (Fischer and Körner, *Ber.*, xvii. 101). The reaction is as follows:—

$$(C_6H_5)_2NH + CHCl_3 + ZnO = C_{13}H_9N,HCl + ZnCl_2 + H_2O.$$

of potassium permanganate it has been converted into quinoline-dicarboxylic or acridinic acid.

Acridine is a tertiary amine. It unites with methyl iodide.

SALTS OF ACRIDINE.

Acridine is a feeble base. It forms no carbonate, and its salts are more or less decomposed by boiling with a large quantity of water.

Acridine Hydrochloride, $C_{13}H_9N,HCl$, forms yellow plates. The solution in water exhibits a bluish-green fluorescence, and gives a yellow crystalline precipitate of the *mercuro-chloride*, $(C_{13}H_9N,HCl)_2HgCl_2$, on adding mercuric chloride. With platinic chloride it yields the *chloroplatinate*, $(C_{13}H_9N)_2H_2PtCl_6$, in minute, sparingly soluble, yellow needles.

Acridine Nitrite, $(C_{13}H_9N)_2,HNO_2,H_2O + 2$ *aqua*, is obtained as a yellow flocculent precipitate on mixing solutions of acridine hydrochloride and sodium nitrite. It forms long, yellow, silky needles, melting at 151°, somewhat volatile with steam, slightly soluble in ether or cold water, more readily in hot water, and very soluble in alcohol.

Acridine Sulphite, $(C_{13}H_9N)_2,H_2SO_3$, is precipitated in yellowish-red or brownish needles, very slightly soluble in water, on mixing solutions of sodium sulphite and acridine hydrochloride, and adding hydrochloric acid.[1]

Acridine Picrate, $C_{13}H_9N,C_6H_3(NO_2)_3$. This compound is obtained as a canary-yellow precipitate, consisting of minute, yellow, prismatic needles, which melt with blackening at 208°. It is almost wholly insoluble in cold, and is partially decomposed by boiling water; it is but slightly dissolved by alcohol or benzene even when boiling. Acridine has been suggested by Anschütz (*Ber.*, xvii. 438; *Jour. Soc. Chem. Ind.*, iii. 234) as a suitable reagent for the determination of picric acid, the hydrochloride being used as a precipitant for metallic picrates, and a solution of the free base in benzene for the picric acid compounds of hydrocarbons.

HYDROACRIDINE. DIHYDROACRIDINE. $C_6H_4\left\{\begin{matrix}CH_2\\NH\end{matrix}\right\}C_6H_4$.

This substance is formed (together with a white substance insoluble in alcohol) by the reduction of acridine in alcoholic solution by sodium-amalgam. It forms prisms melting at 169°, insoluble in water, slightly soluble in cold alcohol, very soluble in hot alcohol or ether. It dissolves in concentrated sulphuric acid, and is precipitated unchanged on dilution with water. Argentic and cupric

[1] Before adding acid, the liquid contains the compound $C_{13}H_9N$ $NaHSO_3$, which forms colourless easily soluble prisms.

oxides reconvert it into acridine. Hydroacridine is the analogue of piperidine (page 106) and tetrahydroquinoline (page 119).

PHENANTHRIDINE. $\left\{ \begin{array}{l} C_6H_4.CH: \\ C_6H_4.N: \end{array} \right\} \Big\}$

Phenanthridine is isomeric with acridine, bearing the same relation to phenanthrene that acridine bears to anthracene (Pictet and Ankersmit, *Ber.*, xxii. 3339; *Jour. Soc. Chem. Ind.*, ix. 280). It melts at 104° and boils about 360°. Phenanthridine presents the closest resemblance to acridine, the chief difference being in its behaviour with reducing agents, for, while acridine yields on reduction a non-basic derivative, phenanthridine gives a hydro-base, which crystallises from alcohol in white needles melting at 100°, and is converted by nitrous acid into a nitrosamine. The *mercuro-chloride* of acridine melts at 225°; the corresponding compound of phenanthridine at 190°. On adding sodium sulphite to a solution of the hydrochloride of acridine, a precipitate of reddish-brown needles is produced, while phenanthridine yields no precipitate.

VEGETABLE ALKALOIDS.

The term "alkaloid" was originally applied to the various basic principles existing naturally in plants. As the number of known animal bases increased in number, it became necessary to describe the plant-bases as "vegetable alkaloids" to distinguish them from the alkaloids of animal origin. But with the advance of synthetical chemistry, and the study of coal-tar products, an enormous number of new bases were prepared, and the restriction of the term alkaloid to the natural plant-bases became still more difficult. Discoveries in recent years have clearly established the fact that many of the plant-bases are related to pyridine or quinoline, and several of the alkaloids have been obtained by actual synthesis from pyridine or its derivatives. In other cases, such as cinchonine and strychnine, the actual synthesis of the alkaloid has not hitherto been effected, but the relationship of the bases to pyridine and quinoline is not less certain. On the other hand, some of the plant-bases stand in much closer relation to uric acid and the bases found in the animal organism than they do to the other plant-bases. Thus caffeine and theobromine are undoubtedly uric acid derivatives, while quinine and morphine show no relation to uric acid, being evidently pyridine derivatives.

Königs has proposed to restrict the term "alkaloid" to bases belonging to the second of these classes, and to define alkaloids as "those organic bases found in the plant kingdom which are pyridine derivatives," and it seems probable that this proposal will gradually be adopted, at least in effect.

With the exception of a limited number of volatile alkaloids (*e.g.*, nicotine, conine, sparteine), the plant-bases contain oxygen in addition to carbon, hydrogen, and nitrogen. They are analogues of ammonia, not ammonium bases; that is, they combine with hydrochloric acid and other acids without elimination of water.

The names of the alkaloids are now usually made to terminate in *ine*, and it is very desirable that this termination should be

strictly confined to bodies of a basic nature.[1] The termination *ia* is still employed for a few of the vegetable alkaloids (*e.g.*, morphia), and by some American writers for certain other alkaloids. The class of bodies known as glucosides—some of which are described in an appendix to this chapter, as, from an analytical point of view, they present some similarity to the alkaloids—should receive names having the termination *in*.

The true vegetable alkaloids or plant-bases are very numerous. Many of them are but imperfectly known, while others (*e.g.*, morphine, quinine, strychnine) have been studied very completely.

The alkaloids as a class are found in all parts of plants, though in some cases the occurrence of particular alkaloids is curiously restricted to certain portions of the plant. Similarly, many of the alkaloids have been met with only in plants of a particular genus or family, and in some cases appear to be characteristic of a single species.[2]

The vegetable alkaloids are in many cases intensely poisonous (*e.g.*, aconitine, veratrine, strychnine), while others, as the alkaloids of coffee, cocoa, and cinchona bark, produce characteristic physiological effects. The large majority of them have a bitter taste.

With the exception of the non-oxygenated volatile bases, nearly

[1] The misuse by chemists of the termination *ine* has caused great confusion, which its employment to designate indefinite commercial products has increased. There is no excuse for writing benz*ine*, paraff*ine*, naphthal*ine* or gelat*ine*; and glycer*ine* is also an undesirable title. The recommendations on nomenclature made by the Publication Committee of the *Journal of the Chemical Society* deserve more attention than they have hitherto received.

[2] J. M. Maisch (*Pharm. Jour.* [3], xxi. 982; from *Amer. Jour. Pharmacy*) states that "among the acotyledons it is almost exclusively the class of fungi which in its different groups produces alkaloids, quite distinct, as a rule, in composition and effect, from those generated within the living tissue of phanerogams. Such alkaloids are in nearly all cases confined to a single species, genus or tribe, and only in rare instances have been met with in several orders. Thus berberine exists in plants of the *Ranunculaceæ*, *Anonaceæ*, *Menispermaceæ*, *Berberidaceæ*, *Rutaceæ*, and *Leguminosæ*; and caffeine in the orders of *Rubiaceæ* (coffee), *Ternstromiaceæ* (tea), *Sapindaceæ* (guarana), *Sterculiaceæ* (colo and cacao), and in *Ilicineæ* (maté, &c.). But colchicine has only been observed in colchicum; veratrine and jervine in veratrum; piperine in certain peppers; quinine and allied alkaloids in cinchona and remijia; strychnine and brucine in strychnos; morphine and congeners in opium, and one or two of these compounds also in other poppies; sanguinarine in a few *Papaveraceæ;* pilocarpine, physostigmine, and cocaine (?), each only in a single species; aconitine and near relatives in several aconites; nicotine in species of tobacco, &c." The mydriatic alkaloids of the *Solanaceæ* are widely distributed throughout the order.

all the vegetable alkaloids are solid at the ordinary temperature. They are in most cases practically fixed, though caffeine and a few others may be sublimed.

Many of the vegetable alkaloids are powerfully alkaline in reaction, neutralise acids perfectly, and form well-defined and crystallisable salts. In other cases the basic character is only feebly marked, no acetates existing, and even the compounds with the stronger acids being decomposed by mere dilution with water.

Except the volatile bases, the vegetable alkaloids are, with few exceptions (*e.g.*, curarine, colchicine), very sparingly soluble in water, and are consequently precipitated, more or less perfectly, on adding caustic potash or soda to the solutions of their salts. In some cases the precipitated alkaloid is soluble in excess of the precipitant. The plant-bases are nearly all dissolved by alcohol (except rhœadine and pseudomorphine), and, as a rule, with great facility. The salts of the alkaloids are usually more soluble in water than the bases themselves, and, as a rule, dissolve also in alcohol. This is true of the sulphates and other classes of alkaloidal salts, the metallic analogues of which are not soluble in alcohol.

Certain classes of double salts of the alkaloids (*e.g.*, chloroplatinates, mercuro-iodides) are, as a rule, very insoluble in water (compare pages 138, 143).

Solvents immiscible with water differ considerably in their action on alkaloids. The free bases are for the most part soluble, especially in chloroform and amylic alcohol, but in the great majority of cases the alkaloidal salts are insoluble in such menstrua. As, however, the salts of the alkaloids of low basic character are decomposed by excess of water, the solutions of these salts often behave with immiscible solvents in the same manner as the free bases (compare pages 158, 159).

CLASSIFICATION OF ALKALOIDS.

The plant-bases are conveniently studied in groups, as it is found that the alkaloids of a certain order or family of plants present more or less general resemblance in properties and composition. Thus the various alkaloids of cinchona bark, of opium, of the aconites, &c., present close analogies among themselves. Other alkaloids do not readily admit of being thus grouped, and when of sufficient importance will be described in separate sections.

In describing the plant-bases the following general arrangement will be adopted:—The general reactions and methods of extracting and purifying alkaloids as a class will first be considered, after

which the existing knowledge of their constitution will be discussed. The non-oxygenated volatile bases will then be described. Then will follow sections on the more important saponifiable alkaloids, such as the aconite and mydriatic alkaloids, and the bases of coca. The opium bases will be next considered, and then strychnine and its allies. The cinchona bases will be treated in the next section, which will be followed by one on caffeine and its allies. Such of the alkaloids as have not been described under any of the foregoing classes, and which are of sufficient importance, will then be described. In an appendix to the chapter some of the more important vegetable bitter principles of non-basic character will be shortly described.

GENERAL REACTIONS OF ALKALOIDS.

The plant-bases present more or less general resemblance in their behaviour with certain reagents, and hence their general reactions are classified in the following sections.

Reactions of the Alkaloids with Acids.

As bodies of basic character, the alkaloids combine with acids to form salts, which in many cases are crystallisable and more or less characteristic. They are mostly soluble in water and alcohol (including the sulphates), but insoluble in chloroform, ether, &c. Certain of the salts of the alkaloids are sufficiently insoluble to allow of the precipitation of the bases for purposes of determination. Instances of this occur with the picrate (berberine, cinchonine, quinine), acid tartrate (cinchonidine), hydriodide (quinidine), chromate (strychnine), hydroferrocyanide (strychnine), periodide (quinine, atropine), chloroplatinate (berberine), aurochloride (aconitine), and mercuro-iodide (strychnine, emetine, colchicine).

TITRATION OF ALKALOIDS.—In their behaviour with indicators of neutrality, the alkaloids present some remarkable differences of behaviour from inorganic bases. The neutral salts of strychnine, quinine, morphine, codeine, conine, nicotine, and other strongly basic alkaloids, are without action on *litmus*, and these alkaloids can be titrated with standard acid and litmus, just like the inorganic bases, except that their high combining weights intensify the effect of the errors of manipulation. Some of the feebler alkaloids, including narceine, narcotine, and papaverine, have no action on litmus, their salts behaving exactly like a corresponding amount of free acid.

The salts of the alkaloids with mineral acids are generally

neutral to *methyl-orange*, which indicator can therefore be used to detect and determine any free acid present.[1]

On *phenolphthaleïn* the great majority of the alkaloids have no action. Hence, after neutralising any free acid with the help of methyl-orange, the acid in combination with the alkaloid present can in most cases be ascertained by titration with standard alkali and phenolphthaleïn, and where the combining weight of the alkaloid is known its amount can be calculated from the result of the same titration. The alkaloids to which the process is not applicable are, so far as at present known, atropine, homatropine, hyoscyamine, hyoscine, and, according to Plugge (*Arch. Pharm.*, [3], xxv. 45), the volatile alkaloids conine and nicotine. In the cases of brucine, morphine and thebaine, a red coloration is obtained somewhat before the end of the reaction, but a little experience is stated to surmount this difficulty. Morphine acts as an acid to *Poirrier's soluble blue* (CLB), probably owing to the presence of the two hydroxyl groups (M. R. Engel, *Compt. Rend.*, cii. 214).

Lacmoïd has been used by Van Itallie (*Analyst*, xiv. 118) for the titration of certain alkaloids, including atropine, hyoscyamine and conine, the hydrochlorides of which are stated to be neutral to this indicator.

Rosolic acid has been employed by E. Dieterich (*Pharm. Jour.*, [3], xvii. 888) for the determination of the alkaloids in extracts of aconite, belladonna, hyoscyamus, conium, and nux vomica, but his results leave the value of the indicator somewhat in doubt.

Many of the alkaloids are more or less changed when heated

[1] In titrating an alkaloid with methyl-orange, it is rarely convenient to employ an aqueous solution of the base. A solution of the alkaloid in proof or rectified spirit is generally suitable, and the indicator is fairly sensitive under such conditions. But when the alkaloid is much coloured, as is frequently the case in the assay of the bases directly extracted from their sources, it becomes difficult or impossible to observe the end of the reaction. Under such circumstances, the writer has overcome the difficulty by dissolving the alkaloid in a little ether, and placing the solution in a small stoppered cylinder, together with a few centimetres of water, coloured with a drop of methyl-orange solution (1:1000). On then gradually dropping in the standard acid and agitating thoroughly after each addition, it is easy to observe the end of the reaction, as the colouring-matter remains in the upper ethereal stratum, and presents a marked contrast to the red colour of the aqueous liquid. By operating in this manner and employing $\frac{N}{50}$ hydrochloric acid, the author has obtained perfectly satisfactory estimations of aconitine, &c., even when working on as little as 0·030 gramme.

with *dilute acids*, in many cases suffering hydrolysis (*e.g.*, atropine, cocaine, aconitine) or being converted into uncrystallisable isomers (*e.g.*, quinine, cinchonine).

Concentrated hydrochloric acid, with application of heat, converts certain of the alkaloids (*e.g.*, morphine, codeine, aconitine) into the so-called apo-bases, with loss of the elements of water. In other instances, one or more methyl-groups are split off (cocaine, colchicine). For colour-reactions, see page 145.

Concentrated nitric acid oxidises and decomposes the great majority of the alkaloids, nitro-derivatives being formed in many cases as intermediate products. In many cases, nitric acid yields more or less characteristic colour-reactions with the alkaloids (page 146).

Concentrated sulphuric acid decomposes the great majority of the alkaloids, the change being sometimes accompanied by interesting colour-reactions (page 145). On applying heat, charring frequently ensues. Strychnine survives to some extent a treatment with concentrated sulphuric acid at 100°.

Reactions of the Alkaloids with Alkalies.

The fixed alkalies, lime, baryta, and ammonia, liberate the plant-bases from their salts, and as the free bases have, as a rule, but limited solubility in water, they are commonly precipitated when the reagent is added to their solutions. The base usually appears as a white, very bulky or flocculent precipitate, often exhibiting a crystalline appearance, either at once or on standing. The precipitates are often hydrated, and sometimes can only be rendered anhydrous with difficulty.

In some cases, the plant-bases when freshly liberated from solutions of their salts by fixed alkalies, alkaline earths, or ammonia, are soluble in excess of the precipitant. Thus morphine and codeine dissolve readily in excess of caustic potash or soda, and slightly in ammonia, and morphine is also soluble in lime and baryta water. Quinine, but not other cinchona alkaloids, dissolves in excess of ammonia, and strychnine also to a limited extent.

The carbonates of the alkali-metals react somewhat peculiarly with the salts of the alkaloids. Few of the alkaloids form carbonates, so that the precipitates produced by alkali-metal carbonates usually consist of the free plant-bases. But the salts of some alkaloids are not precipitated at all by potassium or sodium carbonate (*e.g.*, codeine), and others which are thus precipitated are unaffected by bicarbonates (*e.g.*, strychnine, brucine, atropine, veratrine).

A few of the alkaloids give characteristic colour-reactions when added to fused caustic potash.[1]

Saponification of Alkaloids.

Many of the alkaloids, when boiled with a fixed alkali, baryta, or lime, undergo hydrolysis, with formation of a base of less complex constitution, and the salt of an acid usually belonging to the aromatic series. The change is strictly analogous to the saponification of fats and ethereal salts, and can be effected by boiling with dilute acids as well as by alkalies.

The following equations represent the more important cases of saponification of alkaloids, and show the products of the reaction in each case:—

$C_{33}H_{45}NO_{12}$ Aconitine.	+	H_2O	=	$C_{26}H_{41}NO_{11}$ Aconine.	+	$C_7H_6O_2$ Benzoic acid.
$C_{36}H_{49}NO_{12}$ Pseudaconitine.	+	H_2O	=	$C_{27}H_{41}NO_9$ Pseudaconine.	+	$C_9H_{10}O_4$ Dimethyl-proto-catechuic acid (Veratric acid).
$C_{37}H_{53}NO_{11}$ Veratrine.	+	H_2O	=	$C_{28}H_{45}NO_8$ Verine.	+	$C_9H_{10}O_4$ Veratric acid.
$C_{32}H_{49}NO_9$ Cevadine.	+	H_2O	=	$C_{27}H_{43}NO_8$ Cevine.	+	$C_5H_8O_2$ Methyl-crotonic acid.
$C_{22}H_{23}NO_7$ Narcotine.	+	H_2O	=	$C_{12}H_{15}NO_3$ Hydrocotarnine.	+	$C_{10}H_{10}O_5$ Meconin.
$C_{17}H_{23}NO_3$ Atropine.	+	H_2O	=	$C_8H_{15}NO$ Tropine.	+	$C_9H_{10}O_3$ Tropic acid.
$C_{17}H_{21}NO_4$ Cocaine.	+	H_2O	=	$C_{16}H_{19}NO_4$ Benzoyl-ecgonine.	+	CH_4O Methyl-alcohol.
$C_{16}H_{19}NO_4$ Benzoyl-ecgonine.	+	H_2O	=	$C_9H_{15}NO_3$ Ecgonine.	+	$C_7H_6O_2$ Benzoic acid.
$C_{17}H_{19}NO_3$ Piperine.	+	H_2O	=	$C_5H_{11}N$ Piperidine.	+	$C_{12}H_{10}O_4$ Piperic acid.
$C_{16}H_{23}NO_5$ Sinapine.	+	$2H_2O$	=	$C_5H_{15}NO_2$ Choline.	+	$C_{11}H_{12}O_5$ Sinapic acid.

[1] According to W. Lenz (*Zeitschr. Anal. Chem.*, xxv. 29), out of 72 alkaloids examined, only the following gave characteristic colours when fused with caustic potash, 0·5 milligramme being used in each case:—Quinine, a grass-green and peculiar odour; quinidine, green, becoming yellower and finally brown; cinchonine, brownish-red to violet with green edges, changing to bluish-green; cinchonidine, green, changing to grey; cocaine, greenish-yellow, turning to blue and dirty red on stronger heating.

General Precipitants of Alkaloids.

Alkaloids as a class give precipitates with a considerable number of reagents, especially compounds of some of the heavy metals. The three precipitants of most general applicability are, perhaps, a solution of iodine in iodide of potassium, a solution of phosphomolybdic acid (Somnenchein's reagent), and a solution of the double iodide of mercury and potassium (Mayer's reagent); but neither these nor any other known reagent will precipitate every alkaloid without exception. With the exception of tannin, which should be applied in a strictly neutral or faintly alkaline solution, the precipitants for alkaloids should usually be added to a solution of the base slightly acidulated with sulphuric or acetic acid, but in some cases (as in the precipitation of certain picrates) the solution should be strongly acidulated with sulphuric acid.

Picric Acid, $C_6H_2(NO_2)_3.OH$. *Hager's Reagent.* When used as a test for alkaloids, picric acid is best employed in saturated, cold, aqueous solution (1 : 100). The alkaloidal solution should be rendered distinctly acid with dilute sulphuric acid, except in cases where the alkaloid to be precipitated or sought for is only thrown down in neutral solutions. The precipitated picrates have usually a pale yellow colour, and are either crystalline or become so after a time, the forms in many cases being characteristic.

Picric acid produces no precipitate in solutions (acidulated with sulphuric acid) of aniline, caffeine, conine, morphine, pseudomorphine, solanine, theobromine, or the glucosides; and aconitine, atropine, nicotine, and veratrine are precipitated in concentrated solutions only. Atropine and morphine are precipitated from tolerably concentrated neutral solutions. Copious precipitates are produced by picric acid in acidulated solutions of berberine, colchicine, delphinine, emetine, the cinchona alkaloids, opium alkaloids (except morphine and pseudomorphine), &c. Picric acid is especially suitable for the precipitation of the cinchona alkaloids, and Hager has devised a process of assaying bark based on that fact (see Assay of Cinchona bark). Nicotine, brucine and berberine may also be conveniently estimated by picric acid. They should exist as sulphates in moderately acid solution, and the picric acid be employed as a cold, saturated, aqueous solution, of which 150 c.c. will be necessary to precipitate 1 gramme of the sulphate of a cinchona alkaloid, and twice as much for nicotine sulphate. The following are the limits of dilution at which precipitation occurs, and the characters of the precipitates, according to T. G. Wormley:—

ALKALOID.	CHARACTER OF PRECIPITATE.	LIMIT OF PRECIPITATION.
Nicotine, . . .	Amorphous, changing to crystalline tufts; soluble in nicotine.	1:40,000
Conine, ...	Amorphous, or liquid globules becoming crystalline; soluble in conine and acetic acid.	1:500
Morphine, . .	Amorphous.	1:500
Codeine, ...	Amorphous.	1:2,000
Narceine, . . .	Amorphous; soluble in acetic acid.	1:5,000
Strychnine, . . .	Amorphous, quickly assuming characteristic crystalline forms.	1:20,000
Brucine, ...	Amorphous, becoming crystalline.	1:10,000
Aconitine, . . .	Amorphous; insoluble in ammonia.	1:5,000
Atropine, . . .	Amorphous, changing to very characteristic crystalline forms; soluble in weak acid, including acetic.	1:1,000
Veratrine, . . .	Amorphous; soluble in weak acids, including acetic.	1:5,000
Jervine, ...	Amorphous.	1:1,000
Solanine, . . .	Gelatinous; soluble in excess of picric acid solution.	1:1,000
Gelsemine, . . .	Amorphous.	1:500

The alkaloids may be recovered from their picrates by mixing the moist precipitate with sodium carbonate, drying the mixture, and extracting with alcohol; or the picrate may be shaken with ammonia and a suitable immiscible solvent.

TANNIC ACID precipitates the great majority of the vegetable alkaloids. The precipitates are usually soluble in very weak acids, and in ammonia.

The tannates of aconitine, brucine, caffeine, colchicine, morphine, physostigmine, and veratrine are dissolved by dilute acetic acid and tannate of quinine by somewhat stronger acid. The tannates of aconitine, berberine, (brucine,) caffeine, cinchonine, colchicine, narcotine, papaverine, thebaine, solanine, strychnine, and veratrine resist more or less perfectly the action of cold dilute hydrochloric acid. The tannates of aconitine, physostigmine, quinine, solanine, and veratrine are not redissolved by cold dilute sulphuric acid. Aconitine, physostigmine, and veratrine are completely precipitated by tannic acid from solutions strongly acidulated by sulphuric acid, but only partially from slightly acidulated solutions.

An alkaloid may be recovered from its tannate by mixing the moist precipitate with recently precipitated lead carbonate or hydroxide, drying the mixture, and boiling it with alcohol

or other suitable solvent, which, on evaporation, will often leave the alkaloid in a characteristic crystalline form.

PHOSPHOMOLYBDIC ACID. *Sonnenschein's Reagent.* One of the most valuable general tests for alkaloids, and reagent for separating them from foreign matters, consists of a solution of sodium phosphomolybdate in nitric acid. It is prepared by acidulating a warm solution of ordinary sodium phosphate with nitric acid, and adding an excess of ammonium molybdate solution. The yellow precipitate is separated, washed with water, acidulated with nitric acid, and dissolved in a hot solution of sodium carbonate. The solution is evaporated to dryness and ignited at a low red heat till all ammonium salts are volatilised, the residue moistened with nitric acid, and again ignited. The product, consisting of phospho-molybdate of sodium, is dissolved in ten times its weight of water, and one measure of strong nitric acid (sp. gr. 1·42) added to every ten measures of the solution.

Sonnenschein's reagent gives yellow, usually amorphous, precipitates with nearly all alkaloids, and as most of the precipitates are very insoluble, a negative reaction with the phosphomolybdic solution affords in many cases a positive proof of the absence of alkaloids; but, on the other hand, ammonium salts and other non-alkaloidal bodies are also precipitated by Sonnenschein's reagent. The phosphomolybdates are decomposed by ammonia, in some cases with production of a white precipitate of the liberated alkaloid, which can usually be dissolved by agitation with a suitable solvent, *e.g.*, chloroform, ether, benzene, amylic alcohol; but when the alkaloid is readily oxidisable, treatment of the phosphomolybdate with ammonia is attended with the blue or green coloration indicative of reduced molybdic acid. This occurs in the case of aconitine, aniline, atropine, berberine, codeine, colchicine, conine, morphine, nicotine, physostigmine, &c. Where such reaction occurs the alkaloid is best recovered by mixing the moist phosphomolybdate precipitate into a paste with potassium or sodium carbonate, and extracting with strong alcohol.

PHOSPHOTUNGSTIC ACID, *Scheibler's Reagent*, is used in a similar manner to Sonnenschein's phosphomolybdic solution, and gives very similar reactions with alkaloids. It is prepared by dissolving 100 parts of sodium tungstate and 60 to 80 parts of sodium phosphate in 500 parts of water, and adding nitric acid to acid reaction; or ordinary sodium tungstate may be digested with half its weight of phosphoric acid of 1·13 specific gravity, and allowed to stand for some days, when phosphotungstic acid will separate in crystals. Scheibler's reagent precipitates 1 : 200,000 solution of strychnine and 1 : 100,000 solution of quinine. The alkaloids

may be recovered from their phosphotungstates in the same manner as from their phosphomolybdates (see above).

Metatungstic Acid, *Silicotungstic Acid* (R. Godeffroy), and *Phosphoantimonic Acid* (Schultze) have been proposed as precipitants of alkaloids, but the advantages claimed for them have not led to their general adoption.

BROMINE dissolved to saturation in strong *hydrobromic acid* has been recommended as a general reagent for alkaloids by T. G. Wormley. It is probable that hydrochloric acid might be substituted for the hydrobromic acid without detriment to its efficacy. *Wormley's Reagent* produces yellow amorphous precipitates in solutions of many alkaloids, and crystalline precipitates with meconin (moderately strong solutions), atropine, hyoscyamine and veratrine, the microscopic appearance of the precipitate being in each case characteristic.[1]

IODINE dissolved in a solution of *potassium iodide*, *Wagner's Reagent*, yields reddish or red-brown precipitates with nearly all the alkaloids, even in very dilute solutions. The precipitates are formed more readily in solutions acidulated with sulphuric acid, and when applied under these conditions the reagent is in effect iodised hydriodic acid. Excess of the reagent should be avoided. The quantity used should not be sufficient to colour the solution yellow. Precipitation is so general, and occurs in such dilute solutions, that a negative reaction is conclusive proof of the *absence* of ordinary alkaloids, though precipitation is not conclusive proof of the *presence* of an alkaloid. The precipitates from aqueous solutions are usually amorphous, though codeine, narceine, and strychnine are exceptions. In alcoholic solutions the precipitates are sometimes not formed, or are deposited very slowly; but when produced, they are often of different character from those yielded in aqueous solutions, and in some cases are crystalline. The precipitates are mostly poly-iodides of the alkaloids, the formulæ in some cases being very complex. Thus with quinine there is first a formation of BHI,I; with more of the reagent, BHI,I_4 is obtained; while in alcoholic solution, in presence of free sulphuric acid, and

[1] C. L. Bloxam (*Chem. News*, xlvii. 215) has pointed out that certain of the alkaloids give characteristic colour-reactions when bromine-water is added drop by drop to their solutions in dilute hydrochloric acid. Thus, brucine is stated to yield a violet colour, and strychnine the same on boiling; narcotine a rose pink, and the same with quinine, changed in the latter case to the characteristic grass-green colour on adding ammonia. With excess of bromine, strychnine, brucine and narcotine readily give yellow precipitates; whilst quinine, morphine and cinchonine are only precipitated with difficulty or from strong solutions.

with an excess of the reagent, the curious iodo-sulphate of quinine or herepathite, $B_4,3H_2SO_4,2HI,I_4+3$ aq., is produced. Atropine, strychnine, berberine, and piperine are among other alkaloids giving characteristic compounds with Wagner's reagent. The alkaloids may be recovered from their polyiodides by treating the precipitate with sulphurous acid, a sulphite and dilute sulphuric acid, or sodium thiosulphate, and then adding an alkali and shaking with a suitable immiscible solvent. Treatment with sodium thiosulphate ("hyposulphite"), avoiding excess, is a convenient means of purifying the polyiodides from co-precipitated foreign matter. The reduced solution is filtered and again treated with Wagner's reagent, when the polyiodide is obtained in a condition of purity.

The strength of Wagner's reagent may vary within wide limits. Ordinary decinormal solution of iodine is of suitable strength, or a solution containing 20 grammes of iodine and 50 of potassium iodide per litre may be used.

POTASSIO-IODIDE OF CADMIUM, *Marmé's Reagent*, employed in solutions acidulated with sulphuric acid, gives with alkaloids precipitates which are at first amorphous, but which subsequently become crystalline. They are soluble in alcohol, and in excess of the cadmium solution.

POTASSIO-IODIDE OF BISMUTH, *Dragendorff's Reagent*, is best made by mixing 16 measures of the *B.P.* solution of citrate of bismuth with 1 of strong hydrochloric acid (sp. gr. 1·16), and adding iodide of potassium equal in weight to the hydrochloric acid used (J. C. Thresh). The resulting liquid has an orange colour, and when added to solutions of alkaloids, strongly acidulated with sulphuric acid, forms orange-red precipitates, which appear to be, in most cases, wholly insoluble in cold water. The following are the limits of delicacy, according to J. C. Thresh (*Pharm. Journ.*, [3], x. 641, 809):—Strychnine, 1 in 250,000; quinine, 1 in 200,000; quinidine, 1 in 150,000; cinchonidine, 1 in 125,000; narcotine, 1 in 50,000; brucine and aconitine, 1 in 40,000; atropine, 1 in 25,000; morphine and narceine, 1 in 20,000; codeine, 1 in 17,500; apomorphine, 1 in 12,500; berberine, 1 in 6000; caffeine, 1 in 3000. (See also F. Mangini, *Gazetta*, 1882, 155; *Journ. Chem. Soc.*, xlii. 900.)

POTASSIO-MERCURIC IODIDE, *Mayer's Reagent*, is prepared by dissolving 6·775 grammes of dry crystallised mercuric chloride and 25 grammes of pure potassium iodide separately in water, mixing the solutions so obtained, and diluting the mixture to 1 litre. The solution thus obtained is $\frac{N}{20}$ normal, and of convenient strength for general use, though of only one-half the

strength originally proposed by F. F. Mayer[1] (*Chem. News*, vii. 159).

Mayer's Solution precipitates the great majority of alkaloids, and in some cases from very dilute solutions. Applied, as it always should be, to solutions rendered distinctly acid by hydrochloric or sulphuric acid, ammonia does not interfere; but the solution to be tested must not be more than slightly alcoholic, and must not contain acetic acid. The precipitates yielded by alkaloids with Mayer's solution are usually yellowish-white in colour, and curdy or flocculent. They are more or less soluble in alcohol, ether, acetic acid, iodides, and sometimes in an excess of the reagent. Certain other organic matters besides alkaloids are also precipitated by Mayer's solution, which therefore loses much of its value when applied to unpurified solutions.

Mayer's solution is chiefly valuable as a means of making an approximate volumetric determination of the alkaloid present in a solution; but unfortunately the composition of many of the precipitates obtained with it varies to a serious extent with the concentration of the solution, the proportion of the acid present, and the excess of the reagent.

With strychnine, the composition of the precipitate produced by Mayer's solution approximates to BHI,HgI_2; with morphine it appears to be a variable mixture of $B(HI)_4,(HgI_2)_3$ and $B(HI)_6,(HgI_2)_3$; while with quinine the precipitate is not far from the composition $B_2(HI)_3,(HgI_2)_3$. These formulæ refute the statement made by Mayer, and reproduced by various writers, that the precipitates are of definite composition, containing either 1, 2, or 3 molecules of the base. It has been proved by Lyons that the precipitates nearly always contain a smaller proportion of mercury (often less than three-fourths) than has been assumed to be present in them. The subject has also been investigated by A. B. Prescott (*Chem. News*, xlv. 114, 123).

If Mayer's reagent be added till precipitation ceases, there will always be a large excess of the reagent present. This excess bears a relation to the dilution of the liquid, and the more dilute the solution, the larger the volume of Mayer's solution requisite to

[1] A. B. Prescott has pointed out (*Chem. News*, xlv. 114, 123) that the proportions of mercuric and potassium iodide used in making Mayer's solution correspond to HgI_2+6KI, which might be supposed to react to form $2KI,HgI_2+2KI+2KCl$; but the reactions of the solution point rather to the formula $KI,HgI_2+3KI+2KCl$. Nevertheless, the proportion of potassium iodide cannot be greatly reduced without precipitation of mercuric iodide; but a permanent solution can be obtained with mercuric chloride, potassium iodide, and potassium bromide, used in the proportion indicated by the formula $HgCl_2+4KI+KBr$.

effect complete precipitation. Hence, in order to render titration with Mayer's solution of any value, it is essential that the solutions operated on shall be nearly of uniform strength, and that the reagent be added in exactly the same manner. It is further desirable, whenever possible, to make an experiment, side by side with the alkaloidal solution, with a known weight of the same alkaloid in a state of purity, so as to avoid all assumption as to the behaviour of the volumetric solution with the alkaloid in question.

The following is the usual method of performing the titration of an alkaloid with Mayer's solution :—The solution, which should be distinctly acidulated, and contain, as a rule, 0·5 per cent. of the alkaloid, is treated with Mayer's solution as long as a distinct precipitate is produced. As there is no definite end-reaction, and no satisfactory indicator has been as yet devised,[1] it is necessary to filter a portion of the solution to ascertain if the precipitation is complete. A minute filter, about half an inch in diameter, supported on a ring of platinum-wire, may be used. A drop or two of the filtered liquid [2] is placed on black glass, or on ordinary glass on black paper, and a drop of the volumetric solution added from the burette, when the faintest turbidity will be readily perceived. Before the end of the titration, all the trial-filters and test-drops are returned to the solution containing the main quantity of the precipitate.

The end of the reaction is the point at which the Mayer's solution ceases to produce a precipitate, and it is worthy of notice that, before this point is reached, a condition of equilibrium is attained, in which the solution is liable to be precipitated by the addition of either alkaloidal solution or the mercury reagent.

A. B. Lyons has investigated the behaviour of various alkaloids with Mayer's solution, noting the effect of concentration and the volume of the reagent required to precipitate completely a definite weight of alkaloid; in addition, the volume required to produce an *apparent* excess of the mercury reagent (so that the liquid would give a precipitate with more of the alkaloidal solution); and also the actual excess of Mayer's solution used, as estimated from the quantity of mercury present in the solution.

Lyon's results are given in the following table, reproduced from his *Manual of Pharmaceutical Assaying*. The mercurial solution was $\frac{1}{20}$ normal, and 0·1 gramme of alkaloid was employed in each case :—

[1] F. F. Mayer proposed to ascertain the excess of the reagent by titrating back with standard nitrate of silver solution, without filtering, using potassium chromate as an indicator. As pointed out by Lupinski, the suggestion ignores the accumulation of chlorides and iodides in the solution, as also the fact that some of the precipitates react but slowly with nitrate of silver.

[2] A convenient form of filter-tube for the purpose has been described by F. C. J. Bird (*Pharm. Jour.*, [3], xvii. 826).

Alkaloid.	Solution.		Volume of Reagent in c. c.			Weight of Alkaloid precipitated by 1 c.c. of Reagent.	Weight of Fresh Precipitate after drying at 100° C.
	Condition.	*Strength.*	For apparent *excess.*	For complete *precipitation.*	Used in excess.		
Aconitine,	...	1 : 200	...	7·1	2·0	·0141	·180–·190
Atropine,	...	1 : 200	7·0	13·1	3·0	·0077	·216–·220
,,	...	1 : 400	6·0	14·0	3·5	·0072	...
,,	...	1 : 600	6·0	15·0	3·6	·0067	·192–·200
Berberine,	...	1 : 200	...	3·8	...	·0263	...
,,	...	1 : 400	...	3·9	...	·0257	...
,,	...	1 : 600	...	4·6	...	·0218	·200–·215
Brucine,	Nearly neutral.	1 : 200	...	8·0	1·7	·0125	...
,,	Nearly neutral.	1 : 400	...	8·8	...	·0114	...
,,	Acid.	1 : 400	...	9·8	...	·0102	...
,,	Nearly neutral.	1 : 600	...	9·2	...	·0109	...
Cinchonidine,	...	1 : 100	12·4	13·8	1·0	·0073	...
,,	...	1 : 200	12·4	13·5	0·7	·0074	·330–·375
,,	...	1 : 200	...	15·6	2·6	·0064	...
Cinchonine,	...	1 : 100	...	12·8	0·8	·0078	...
,,	...	1 : 100	...	14·0	1·2	·0072	...
,,	Neutral.	1 : 200	7·9	10·8	...	·0093	·333–·345
,,	Acid.	1 : 200	8·0	14·2	...	·0071	...
,,	Neutral.	1 : 400	8·0	12·4	2·4	·0082	...
,,	Acid.	1 : 400	9·6	14–18	...	·007 to ·0086	...
Cocaine,	...	1 : 200	...	12·8	...	·0078	·246
,,	...	1 : 400	10·0	14·4	4·6	·0069	...
,,	...	1 : 600	...	16·0	5·2	·0063	...
Colchicine,	...	1 : 200	3·2	9·2	...	·0109	·160
,,	...	1 : 400	4·2	11·4	...	·0088	...
,,	...	1 : 600	5·0	12·6	...	·0080	...
,,	...	1 : 800	4·0	14·6	...	·0067	...
Emetine,	...	1 : 200	8·0	9·4	0·4	·0106	·256
,,	...	1 : 400	8·8	10·2	1·0	·0098	...
,,	...	1 : 600	...	10·6	0·6	·0094	...
Gelsemine,	...	1 : 200	5·8	10·4	...	·0096	·185–·200
,,	...	1 : 400	6·5	12·0	...	·0084	...
Hydrastine,	...	1 : 200	...	7·4	...	·0135	·200–·210
,,	...	1 : 400	...	8·0	...	·0125	...
,,	...	1 : 600	...	8·4	...	·0119	...
Hyoscyamine,	...	1 : 200	...	8·5	...	·0116	·220–·250
Morphine,	...	1 : 200	7·0	4·91	...	·0128	·190–·240
,,	...	1 : 400	...	8·9	0·6	·0110	...
Pilocarpine,	...	1 : 200	4·8	16·8	...	·0060	·240–·350
,,	...	1 : 200	...	20·0	...	·0050	...
Quinine,	Neutral.	1 : 200	11·6	16·4	...	·0061	...
,,	Acid.	1 : 200	12·4	18·0	...	·0056	·310–·385
,,	...	1 : 400	12·8	16·8	...	·0060	...
,,	...	1 : 600	12·2	20·0	...	·0050	...
Strychnine,	...	1 : 200	...	11·0	0·6	·0091	·260–·275
,,	Neutral.	1 : 400	11·6	12·0	...	·0084	...
,,	Acid.	1 : 400	11·6	12·2	...	·0082	...
,,	...	1 : 600	11·2	11·9	0·6	·0087	...

From a study of this table by Lyons, it appears that while a notable excess of the reagent is generally needed to effect complete precipitation, the weight of the precipitate is in many cases considerably below the amount indicated by theory. Better results in this respect are obtainable by allowing the liquid with the suspended precipitate to stand for some time. Lyons states that, under these circumstances, the atropine precipitate becomes dense

and crystalline, and in part adheres to the beaker, in which it can be washed by decantation, dried, and weighed, the amount thus found falling little short of the theoretical weight of 0·245 gramme for 0·100 of alkaloid.

The following data showing the behaviour of alkaloids with Mayer's solution are tabulated from the descriptions of Dragendorff (*Plant-Analysis* and *Analyse Chimique de quelques Drogues Actives*):—

Alkaloid.	*Dilution of Solution.*	*Milli-grams of Alkaloid Ppted. by 1 c.c.*	*Correction for Solubility. Mgrms. for 10 c.c. Filtrate.*	*Observers.*	*Conditions of Precipitation.*
Aconitine,	...	13·45	0·5	Dragendorff.	...
Pseudaconitine,	...	19·4	...	,,	...
Atropine,	1 : 200	4·85	...	,,	Ample time required for precipitation.
,,	1 : 330	4·14	0·5	,,	
Hyoscyamine,	1 : 200	3·49	...	,,	...
Emitine,	...	9·45	...	,,	...
Conine,	1 : 200	6·25	...	,,	Faintly acid only. KCl present.
,,	...	2·10	...	Mayer.	
Nicotine,	...	2·02	...	Dragendorff.	Sol. strongly acidulated.
Strychnine,	...	8·35	...	,,	...
,,	...	8·30	...	Mayer.	Sol. faintly acid only.
Brucine,	...	9·85	...	Dragendorff.	
,,	...	11·65	...	Mayer.	Sol. strongly acid.
Colchicine,	1 : 600	15·85	...	Dragendorff.	
Morphine,	...	10·00	...	,,	...
Narcotine,	...	10·65	...	,,	...
Veratrine,	...	14·80	0·7	Masing.	Slightly acid solution.
,,	...	13·50	...	Mayer.	
Sabadilline,	...	18·70	0·5	Masing.	
Sabatrine,	...	16·63	0·4	,,	
Physostigmine,	...	6·87	1·0	,,	...
Berberine,	...	21·25	...	Beach.	...
Chelidonine,	...	8·37	...	Masing.	...
Sanguinarine,	...	7·42	...	,,	...
Quinine,	...	5·40	...	...	...
Cinchonine,	...	5·10	...	...	...

Hereth (*Pharm. Record*, 1886, page 209) has proposed an improved method of operating with Mayer's solution, which allows time for the precipitate to fully form. A number of equal portions of the solution to be tested are treated with volumes of the mercurial solution, regularly increasing by 0·1 c.c., and allowed to stand eight or ten hours. Trial-portions of each mixture are then removed and tested with two drops of Mayer's solution, when a particular mixture will be found to have the mercurial solution in slight excess, while in the previous mixture it is deficient. Obviously, the true amount lies between the two, and it is easy to ascertain the exact volume required.

Strychnine and quinine are among the alkaloids yielding the most insoluble precipitates with Mayer's solution. With atropine

and morphine the reaction is far less delicate, and caffeine and theobromine are not precipitated at all.

MERCURIC CHLORIDE, $HgCl_2$, gives, with certain alkaloids, precipitates of which the crystalline form or melting-point is characteristic. As a rule, the precipitates have the constitution $B_2H_2HgCl_4$, and are less insoluble than those produced by Mayer's reagent.

AURIC CHLORIDE, $AuCl_3$, gives yellow precipitates of alkaloidal aurochlorides or chloraurates with hydrochloric acid solutions of many of the alkaloids. The double salts precipitated are often very insoluble. They usually contain $B,HCl,AuCl_3$ or $BHAuCl_4$, though this formula is not without exception. Auric chloride has the advantage that ammonium salts and the simpler amides are not precipitated by it; but the precipitates are unstable, the yellow colour in many cases rapidly changing to reddish brown, while the supernatant liquid occasionally acquires an intense red colour.

PLATINIC CHLORIDE, $PtCl_4$, is a useful reagent for many alkaloids, with the hydrochlorides of which it combines to form chloroplatinates or platinochlorides. In some instances, these double salts have the formula BH_2PtCl_6, and in other cases they contain $B_2H_2PtCl_6$, while in a few instances more complex formulæ have been attributed to them. It is sometimes stated that the alkaloids containing N_2 in the molecule form chloroplatinates of the first formula, while in the case of bases having only one atom of nitrogen the platinum salts contain two atoms of alkaloid; in other words, that the ratio of N : Pt is constantly as 2 : 1. This, however, is far from being the case, for alstonine, gelsamine, aspidospermine, paytine, strychnine, pilocarpine, and numerous other bases containing N_2 agree with the opium bases, berberine, cevadine, atropine, and others containing N in forming platinum salts of the formula $B_2H_2PtCl_6$. In addition, many of the cinchona-bases form platinum salts of both series.

The chloroplatinates of the alkaloids vary in colour from pale yellow, through orange and red, to brownish red. They are mostly sparingly soluble in water, and hence are usually formed as precipitates on adding platinic chloride to a solution of the alkaloid acidulated with hydrochloric acid. The similar behaviour of potash and ammonia diminishes the value of the test. Xanthine, caffeine, colchicine and pelletierine are among the alkaloids not precipitated. Of the rest, the chloroplatinates of quinine, cinchonine, morphine and strychnine are among those dissolved by hydrochloric acid. The melting-points of the alkaloidal chloroplatinates are often characteristic.

POTASSIUM PERMANGANATE, $KMnO_4$, produces characteristic

reactions with certain of the alkaloids. Beckurts and List have examined the behaviour of a number of them, by adding a decinormal solution of the reagent, drop by drop, to a cold saturated aqueous solution of the hydrochloride of the base. Immediate reduction of the permanganate, with separation of brown manganese oxide, was observed with the hydrochlorides of quinine, cinchonidine, cinchonine, cinchonamine, brucine, veratrine, colchicine, conine, nicotine, aconitine, physostigmine, codeine, and thebaine. The solutions of atropine, hyoscyamine, pilocarpine, berberine, piperine, and strychnine were coloured red, the reagent being only gradually reduced.

With morphine hydrochloride the permanganate produced a white crystalline precipitate of oxydimorphine, which, when filtered off and dried, could be recognised by its characteristic reactions. Apomorphine hydrochloride immediately reduced the reagent, with production of an intense green colour.

On adding a few drops of a decinormal solution of potassium permanganate to a concentrated solution of narceine hydrochloride a reddish precipitate is immediately formed, which is very stable in the cold and in the absence of an excess of the reagent, but is decomposed on heating or by addition of more permanganate. Solutions of papaverine hydrochloride, and of narcotine if diluted with hydrochloric acid, at first behave similarly; but the precipitates are much less stable than narceine permanganate, and soon discolour and decompose with separation of brown manganese oxide.

F. Geisel (*Pharm. Zeit.*, 1886, p. 132) has pointed out that cocaine gives a comparatively stable permanganate, which forms a purple-violet precipitate of characteristic microscopic appearance. The precipitate forms only slowly in dilute solutions, and undergoes gradual decomposition.

Colour-Reactions of Alkaloids.

Many of the alkaloids give brilliant, and in some cases characteristic, colorations when treated with appropriate reagents. When possible, the reaction should be compared with that yielded by the pure alkaloid treated side by side with the sample. The reagents which have been proposed as colour-tests for alkaloids are very numerous, and have not always been chosen or applied with discretion, nor with a due regard to purity. The colour-reactions may be classified as:—(1) Those produced by dehydrating agents, such as strong sulphuric acid, phosphoric acid, and zinc chloride;[1] (2) those given by oxidising agents

[1] In using zinc chloride, Czumpelitz directs that the substance to be examined should be first carefully dried, moistened with a solution of 1 gramme

not of themselves yielding colours, such as nitric acid, chlorine, bromine, and bleaching powder; or sulphuric acid and oxidising agents, such as potassium chlorate, perchlorate, and permanganate; (3) those given by oxidising agents which themselves yield a coloured product by reduction, such as iodic acid and reagents containing chromic, molybdic, tungstic, and vanadic acids; (4) and colorations produced by certain special reagents, such as ferric chloride, hydrochloric acid, sulphuric acid and sugar,[1] &c.

As a rule, the best method of observing the colour-reaction of an alkaloid is to apply a drop of the reagent by means of a pipette or glass rod to a minute fragment of the solid alkaloid placed on a porcelain plate or in a flat porcelain dish. An alkaloidal residue obtained by the evaporation in a porcelain capsule of an alcoholic, ethereal, chloroformic or other solution may be very conveniently employed for observing colour-reactions.

Fused Caustic Potash gives a few interesting colour-reactions with alkaloids (see foot-note, page 133).

Concentrated Hydrochloric Acid gives colour-reactions with a few alkaloids. Thus, *reddish* colours are yielded with physostigmine, sabadilline, sabatrine, veratrine, and veratroïdine; and a yellow with thebaine. On addition of chlorine-water after hydrochloric acid, berberine gives a red colour. Nicotine yields an amorphous hydrochloride and conine a crystalline salt, on evaporating the solution in hydrochloric acid.

Concentrated Sulphuric Acid gives colour-reactions with a number of alkaloids, the coloration varying with the degree of heat applied. The following reactions have been observed when the acid is dropped on to the solid alkaloid, without applying heat:—*No colour*, or a faint straw tint only, is yielded by pure aconitine, atropine, caffeine, chelonidine, cinchonidine, cocaine, codeine, hyoscine, hyoscyamine, gelsemine, morphine (purple to brown on warming), nicotine, pilocarpine, quinine, quinidine, staphisagrine, strychnine, and theobromine. *Yellowish* colorations are given by colchicine, gnoscopine, jervine, and by many other alkaloids in presence of impurities. *Reddish* colours are produced either immediately or gradually, with impure aconitine,

melted zinc chloride in 30 c.c. of water, and dried again. If thus treated, strychnine takes a scarlet colour, thebaine a yellow, narceine an olive-green, delphinine a red-brown, berberine a yellow, veratrine a red, quinine a pale yellow, digitalin a maroon, salicin a violet-red, santonin a violet-blue, and cubebin a purple. The presence of brucine prevents the coloration of strychnine, the tinge produced being a dirty yellow (*Giornale Farm. Chim.; Jour. Chem. Soc.*, xlii. 340).

[1] Information respecting this test will be found under "morphine."

apomorphine, brucine (pale rose), cocaine (impure), conine (pale red), gelsemine (impure), meconidine, narceine (changing to black), narcotine (yellowish-red, changing to violet and blue), physostigmine, rhœadine, sabadilline, sabatrine, solanine, taxine, thebaine, veratrine, and veratroïdine. *Bluish* colorations are yielded by cryptopine, curarine (after a time), and papaverine. *Greenish* colours are given by beberine, berberine, emetine (brownish to green), piperine, pseudomorphine, and sometimes by rhœadine.

Some characteristic changes of colour can be obtained by gradually warming the capsule in which the test is being made, by placing it over a small beaker of boiling water. The ultimate result is usually browning and charring of the alkaloid, but the intermediate reactions are often of value.

Many substances besides alkaloids give more or less brilliant colour-reactions with strong sulphuric acid. Thus *red* colorations (often of a brilliant hue) are obtained with amygdalin, columbin, cubebin, elaterin, hesperidin, phloridzin, populin, salicin, sarsaparillin, senagin, smilacin, syringin, and many varieties of tannin.

In applying sulphuric acid as a colour-test for alkaloids, it must be remembered that the presence of a very minute quantity of nitric acid, often present as an impurity, greatly modifies the colorations produced by many of the alkaloids. Thus, if the treatment with sulphuric acid (without applying heat) be followed by the addition of a very minute quantity of nitric acid (at the end of a glass rod drawn out to a point), or a minute fragment of solid potassium nitrate, the following reactions will be obtained:[1] *No colour* with atropine, caffeine, cinchonidine, cinchonine, nicotine, pilocarpine, quinidine, quinine, staphysagrine, strychnine, or theobromine; *red* coloration with brucine, curarine, narcotine (reddish violet or blood-red), physostigmine, sabadilline, thebaine, and veratrine (gradual change to cherry-red). Special and peculiar changes of colour are produced by morphine, codeine, and colchicine, and are described in the respective sections on these alkaloids.

Strong Nitric Acid, of 1·40 to 1·42 specific gravity, gives more or less characteristic colour-reactions with a number of alkaloids. A drop of the acid should be applied by means of a glass

[1] Erdmann applies this test by mixing 6 drops of nitric acid of 1·25 specific gravity with 100 c.c. of water, and adding 10 drops of the dilute acid so obtained to 20 grammes of sulphuric acid. From 8 to 10 drops of the solution so prepared, or *Erdmann's Reagent*, is added to 1 or 2 milligrammes of the solid to be tested, and the colour observed after 20 to 30 minutes.

rod to a minute fragment of the alkaloid, or to a residue left on evaporating a solution on white porcelain. *No coloration* is yielded by aconitine (when pure), atropine, caffeine, cinchonidine, cinchonine, conine, gelsemine (impure, greenish), quinidine, quinine, strychnine, or theobromine. *Yellowish* colours are obtained with impure aconitine (colour varies from yellow to red and brown), codeine (orange-yellow), morphine (yellow to red), narceine, narcotine, papaverine (orange), piperine (orange), rhœadine, sabadilline (yellow), thebaine, and veratrine. *Red* shades are produced by impure aconitine (colour varies from yellow to red and brown), apomorphine, beberine (red to red-brown), berberine (red-brown), brucine (blood-red), papaverine (orange-red), pseudomorphine (orange-red), and physostigmine (gradually). Gelsemine yields a deep bluish *green* residue on evaporation. *Blue* colours are said to be given by colchicine and solanine; and by the glucosides ligustrin and syringin.

SULPHOMOLYBDIC ACID, *Fröhde's Reagent*, affords one of the most useful of the oxidation-tests for alkaloids; but it must be borne in mind that the colours produced are in great measure those of the lower oxides of molybdenum, and that various other bodies besides alkaloids readily reduce molybdic acid with formation of these coloured oxides. The reagent itself, if strongly heated, acquires a blue coloration from reduction of the molybdic acid. Fröhde's reagent is prepared by dissolving 5 milligrammes of molybdic acid or molybdate of ammonium in each 1 c.c. of strong sulphuric acid. *No colour* is produced with atropine, caffeine, cinchonidine, cinchonine, conine, delphinine, hyoscine, hyoscyamine, nicotine, strychnine, or theobromine. *Yellowish* colorations are given by aconitine, colchicine, and piperine. *Reddish* shades of colour are produced by brucine, emetine (red, changing to green), narceine (red, changing to blue), sabadilline (reddish violet), solanine, thebaine (orange), and veratrine (gradual production of a cherry-red colour). *Bluish* colours are given by codeine (gradual production of deep blue), morphine (violet-blue, then dirty green, changing to deep blue), narceine (yellowish brown, changing to red and blue), staphysagrine (violet-brown). *Greenish* colorations are produced by apomorphine (green to violet), beberine (brown-green), berberine (brown-green), emetine (red, changing to green, and turned blue by hydrochloric acid), quinine (pale green), and quinidine (pale green).

Of non-alkaloidal bodies, colocynthin gives slowly a cherry-red colour; elaterin, a yellow; phloridzin, gradually, blue; populin, violet; salicin, violet to cherry-red; and syringin, a blood-red to violet-red coloration.

Sulphovanadic Acid has been recommended by F. Kundrát (*Chem. Zeit.*, xiii. 265; *Jour. Soc. Chem. Ind.*, viii. 421) as a colour-test for alkaloids. The reagent is prepared by dissolving 0·1 gramme of ammonium vanadate in 10 c.c. of strong sulphuric acid. It is stated to give the following reactions, many of which are due to the production of the coloured lower oxides of vanadium, and hence are likely to vary with the proportions of the reagent and alkaloid employed. *No coloration* is produced by caffeine or nicotine. *Brown* by aconitine (light coffee-brown), codeine (greenish brown, becoming darker), morphine, narceine (changing to dirty bluish violet, then gradually reddish brown), piperine (intense reddish brown to black), kairine (dirty pink, quickly changing to dirty light brown and brownish green), solanine (coffee-brown, changing at the edge to purple and in the centre to dirty green, and very gradually becoming an intense violet jelly). *Red* colorations are given by atropine (changing to yellowish red and yellow), brucine (intense blood-red, gradually fading), narcotine (blood-red or purple), and veratrine (brownish red, changing to reddish violet). *Yellowish* or *orange* colours are produced by cinchonine (changing to green), cocaine (orange, froths on dissolving), physostigmine (greenish yellow, then purple, finally yellow-brown), and quinine (changing to bluish green and greenish brown). *Green* colorations are produced by colchicine (changing to greenish brown and coffee-brown), conine (intense green, changing to brown), and quinidine (faint bluish green). *Blue* reactions are produced by antipyrine (greenish blue, gradually becoming bluer), and apomorphine (dark violet blue, rapidly changing through dirty green to reddish and light brown). *Violet* colorations are given by papaverine (gradually changing to bluish green and orange-green), and strychnine (bluish violet, changing to reddish violet, purple, and brilliant red).

Of colorations with non-basic principles the following have been recorded:—Antifebrin, purple, rapidly changing to brown; digitalin, intense brown, with reddish shade; and salicylic acid, brownish green. Picrotoxin and santonin give no coloration with sulphovanadic acid.

Ferric Chloride gives a few characteristic colorations, the most important being the blue reaction with morphine and the blood-red with antipyrine (page 35). A freshly-made mixture of *ferric chloride and potassium ferricyanide* (free from ferrocyanide), both in aqueous solution, has a yellowish brown colour; but in presence of certain alkaloids it is immediately coloured blue (or green) owing to the production of Prussian blue. This reaction was at first regarded as characteristic of the ptomaines or cadaveric bases, but it is produced by any readily oxidisable

alkaloid, and hence is given immediately by morphine, cocaine, aconitine, physostigmine, &c., and after a short time by hyoscyamine, emetine, colchicine, nicotine, and many of the tar-bases.

OXIDATION-COLOUR-REACTIONS are also produced by reagents having a more powerful oxidising action than the foregoing. Thus strong sulphuric acid may be employed in conjunction with potassium nitrate, chlorate, perchlorate, permanganate, bichromate, and ferricyanide; or with metallic peroxides, such as those of manganese (MnO_2), lead (PbO_2), ruthenium (RuO_3), uranium (U_2O_3), and cerium (Ce_3O_4). The most important of the colour-reactions obtained with such reagents are those yielded by strychnine, curarine, gelsemine and aniline, which are fully described elsewhere.

Physiological Tests for Alkaloids.

A large number of the natural alkaloids, if not an actual majority, have well-marked poisonous characters. The symptoms produced are of the varied description, ranging from the narcotism of morphine to the paralysis of conine and the tetanus of strychnine.

In making experiments on animals it is often advantageous to administer the poison by hypodermic injection of a solution of alkaloid in water, or weak spirit acidulated with acetic acid. Such a plan obviates the loss of the poison by vomiting, which sometimes eliminates the greater part of the poison from the system. On the other hand, the subcutaneous injection of small animals is open to certain obvious objections, and in many cases internal administration may be advantageously substituted for it, especially if the animal employed be a rabbit or guinea-pig, and hence not liable to vomit. In many instances, such animals are hopelessly large, and mice, small birds, or frogs must be employed. Wynter Blyth has used blowflies with success in some cases, and occasionally fish are of service. When the poison is to be given internally, the extract or very strong solution should be made up into one or more small pills with oatmeal, which the animal is either induced to eat or forced to swallow. In the case of linnets and other small birds, a drop of the liquid to be tested should be introduced into the open beak by means of a pipette or feather.

In some cases, physiological tests may be advantageously made on human subjects. Besides observing the bitter taste possessed by most alkaloids, the tingling sensation produced on the tongue by aconitine and cocaine can be thus detected.

A marked physiological characteristic of many of the alkaloids, sufficiently striking in some cases to serve as actual evidence of their presence, is their *effect on the pupil* of the eye. The test is

generally made by placing a drop of the alkaloidal solution to be examined, as nearly neutral as possible, on the eye of a rabbit, dog or cat, when, in a time varying from a few minutes to about half an hour, a marked contraction or dilation of the pupil will be observed.

A. The pupil is *dilated* by:—

1. Atropine and belladonna; hyoscyamine and hyoscine, and preparations of henbane and stamonium; solanine; and extracts from solanaceous plants generally.
2. Cocaine, and preparations of coca.
3. Conine, and preparations of hemlock and other umbelliferous plants.
4. Cytisine, and preparations of laburnum.
5. Digitalin, and preparations of foxglove.
6. Gelsemine, and preparations of gelsemium (yellow jesamine).
7. Sparteine, and preparations of broom.
8. Veratrine, jervine, and preparations of hellebore.
9. Hydrocyanic acid and cyanides.

Mydriasis, or dilation of the pupil, is so striking a characteristic of atropine and the isomeric and associated bases that these are often grouped together as the "mydriatic alkaloids." The mydriasis is only observed in the eye to which the alkaloid is applied.

B. The pupil is *contracted* by:—

1. Morphine, and other opium alkaloids and preparations of opium.
2. Aconitine, and preparations of aconite and other members of the *Ranunculaceæ*.
3. Physostigmine, and preparations of the Calabar bean.
4. Strychnine, brucine, and preparations of nux vomica.

A similar effect on the pupil is produced by the poisons when taken internally or hypodermically in sufficient quantities. Sometimes, as in the case of morphine and preparations of opium, the pupils are contracted during the early stages of the poisoning, but dilated subsequently, especially after death. Nicotine and preparations of tobacco in some cases cause contraction, and in others dilation, of the pupil. In poisoning with aconitine alternate contraction and dilation of the pupil is sometimes observed.

ISOLATION AND PURIFICATION OF ALKALOIDS.

The vegetable alkaloids are found in all parts of plants, and in many cases constitute their characteristic active principles. It must not be assumed that the active principle is necessarily of an alkaloidal character, though plants and plant-products, which act primarily on the nervous system, producing tetanus, paralysis, or narcosis (*e.g.*, nux vomica, aconite, opium), owe their activity, as a rule, to the presence of an alkaloid. On the other hand, in plants which act primarily on the muscular system (*e.g.*, digitalis), the active principle is usually of a non-alkaloidal character. Where the action of the plant is emetic, cathartic, or purely astringent, the active principle is usually of a neutral or resinous character; but this statement has some marked exceptions, for ipecacuanha, a typical emetic, owes its activity to the alkaloid emetine.

An alkaloid never exists in a plant in a free state. It is most frequently present as a salt, often an acid salt, of some organic acid, especially malic acid or one of the varieties of tannic acid. In some instances the acid with which the alkaloid is united is peculiar to the plant in question, as, for instance, meconic acid in opium, quinic acid in cinchona bark, and igasuric acid in *nux vomica*. In other cases the alkaloid is combined with an inorganic acid, as is the case, in part at least, with the morphine in opium. The natural forms of combination of the alkaloids are almost invariably readily soluble both in water and in alcohol, but insoluble in ether.

The general action of solvents on the leading constituents of plants will be seen from the following table, which will also serve to indicate the nature of the bodies likely to be co-extracted with the alkaloid when the respective solvents are employed:—

	Water.	*Alcohol.*	*Ether.*
Alkaloidal salts, . .	Soluble.	Soluble.	Insoluble.
Other salts of inorganic acids,	Mostly soluble.	Mostly insoluble.	Insoluble.
Other salts and organic acids,	Soluble.	Soluble.	Mostly insoluble.
Free organic acids, .	Soluble.	Soluble.	Mostly insoluble.
Tannins and colouring matters,	Soluble.	Soluble.	Variable.
Sugars, ...	Soluble.	Soluble.	Insoluble.
Gums and pectous bodies,	Soluble.	Mostly insoluble.	Insoluble.
Albuminoids, &c., .	Soluble.	Insoluble.	Insoluble.
Starch, ...	Soluble in hot water.	Insoluble.	Insoluble.
Cellulose, . . .	Insoluble.	Insoluble.	Insoluble.
Resins, ...	Insoluble.	Soluble.	Variable.
Fixed oils, . . .	Insoluble.	Sparingly soluble.	Soluble.
Essential oils, . .	Insoluble.	Soluble.	Soluble.
Chlorophyll, . . .	Insoluble.	Soluble.	Soluble.

Alcohol is the solvent best adapted for the extraction of alkaloids from plants, which should, of course, be reduced to a suitable condition. The treatment may with advantage be repeated several times, the residue being well pressed between each exhaustion, which is preferably effected by a percolator, or some equivalent arrangement. In the final extraction, the addition of a little sulphuric or tartaric acid is often an advantage, but the amount of acid used should be very limited, and its employment is vetoed in the case of readily changeable alkaloids. Hot water may be substituted for alcohol in some cases. When alcohol has been used for the extraction, it should be removed partially or wholly by gentle evaporation before proceeding to the next stage of the treatment.

The method to be adopted for the isolation of the alkaloid from the infusion or tincture obtained depends much on its nature, and the object of the experiment. Extraction by immiscible solvents permits the detection of small quantities of alkaloids, which defy methods based on precipitation, and hence this principle is very valuable in toxicological investigations; but, on the other hand, the alkaloids so extracted are usually less pure than when isolated by other means.

Where it is intended to attempt the separation of the alkaloid by conversion into an insoluble or nearly insoluble compound, a variety of precipitants are available, each one of which has special advantages in particular cases. But before resorting to these general precipitants, it is desirable, and in many cases absolutely necessary, to remove from the liquid as much as possible of the inert organic matters. The best reagent for this purpose is lead acetate, which should be added gradually to the previously neutralised liquid, as long as a precipitate continues to be produced, avoiding the use of any considerable excess of the reagent. The precipitate having been filtered off, the filtrate should be treated with basic acetate of lead, which in many cases will produce a further precipitate, to be removed by the filter as before. On adding ammonia to the filtrate, a third precipitate will frequently be produced, but it must be remembered that cinchonine and other sparingly soluble alkalies are liable to be thrown down at this stage.[1] (On this account it is undesirable to add basic acetate of lead and ammonia at once, and filter off the joint precipitate.)

[1] The threefold treatment with neutral lead acetate, basic lead acetate, and ammonia in presence of lead acetate causes the precipitation of tannins; most vegetable acids (*e.g.*, malic, tartaric, oxalic); albuminoids, starches, and gums; many glucosides, sugars, and dextrin; and the majority of colouring matters.

The liquid, which should smell distinctly of ammonia, is next evaporated at a gentle heat till the odour of ammonia has disappeared, when the excess of lead is precipitated by a stream of sulphuretted hydrogen or the addition of a moderate excess of dilute sulphuric acid. Of these plans, the first is much to be preferred. The lead sulphide often carries down with it a notable quantity of colouring matter, otherwise difficult to remove, and the excess of sulphuretted hydrogen is easily got rid of by concentrating the filtrate at a gentle heat. When sulphuric acid has been employed to precipitate the lead, the filtrate should be carefully neutralised before attempting to further concentrate the liquid, otherwise the alkaloid may suffer partial or complete decomposition.

The alkaloidal solution, having been purified by the foregoing treatment, may be treated with one of the general reagents for alkaloids, the choice of which will necessarily depend on the nature of the base supposed to be present. Where this is unknown, preliminary tests with various precipitants should be made on small aliquot fractions of the solution. Although other reagents may be preferable in particular cases, the choice will generally lie between one of the following precipitants:—

1. A fixed *alkali*, *carbonate of alkali-metal*, *lime*, or *ammonia*; suitable for precipitating morphine, the cinchona alkaloids, the aconite bases, &c.
2. *Picric acid* (page 134); very suitable for precipitating the cinchona bases, emetine, berberine, and veratrine.
3. *Tannic acid* (page 135).
4. *Phosphotungstic* or *phosphomolybdic acid* (page 136); available for the great majority of alkaloids, and especially for strychnine.
5. *Iodised iodide of potassium* (page 137), which produces very insoluble precipitates with the great majority of alkaloids.
6. *Mayer's solution* (potassio-iodide of mercury) (page 139); valuable for precipitating emetine and the opium bases.

With the exception of tannic acid, which should be applied to the neutral or even faintly alkaline solution of the alkaloid, the reagent should be added to the acidulated solution, sulphuric acid being the most suitable acid to bring the liquid to the proper condition. In most cases precipitation is tolerably rapid, but it is desirable, as a precaution, to wait 24 hours before proceeding with the filtration. This is especially necessary perhaps in the case of precipitants 1 and 2. The alkaloid may be

recovered from the precipitate in the manner described on page 135 *et seq.*

As a rule, the salts of the alkaloids are not soluble in immiscible solvents, and hence when the acidulated solution of an alkaloid is agitated with chloroform, ether, petroleum spirit, benzene, or amylic alcohol, the solvent does not remove the base from the aqueous liquid. This behaviour broadly distinguishes alkaloids from glucosides; but, owing chiefly to their weak basic character and the instability of their salts, caffeine, colchicine, delphinine, narcotine, papaverine, thebaine, and theobromine are partially or wholly removed from their acidulated solutions on agitation with chloroform, while amylic alcohol is stated to extract berberine and veratrine in addition to the above bases.

Extraction by Immiscible Solvents.

The behaviour of the alkaloids, when their acid and alkaline solutions are agitated with immiscible solvents, is of the highest practical value for their isolation and identification.[1]

The immiscible solvents used for the extraction of alkaloids, &c., should be free from any trace of fixed or difficultly volatile organic matter. This is best ensured by shaking the solvent with water slightly acidulated with sulphuric acid, separating the aqueous liquid, and redistilling the immiscible solvent at a moderate temperature—rejecting the last portion. The distillate should then be agitated with water rendered faintly alkaline by caustic soda, and indeed may be advantageously kept in contact with faintly alkaline water. The agitation with water is essential in the case of solvents liable to certain alcohol (*e.g.*, ether, chloroform, amylic alcohol), the presence of which might seriously modify their action.

In using immiscible solvents, it must be borne in mind that extraction is never theoretically perfect with a single treatment. The dissolved body is distributed between the two solvents in proportions which are probably dependent on the relative solubility of the substance in the two media, and the relative quantities of the two media employed. Thus, it may be supposed that if a substance be 99 times more soluble in chloroform than in water, and its aqueous solution be shaken with an equal

[1] The principle appears to have been first adopted by Otto in 1856, who employed ether in his modification of Stas' process for the detection of poisonous alkaloids. In 1856, Rodgers and Girdwood employed the method with chloroform, and in 1861 Uslar and Erdmann recommended the use of amylic alcohol. In 1867, Dragendorff published his well-known elaborate scheme for the separation of plant-principles by immiscible solvents.

measure of chloroform, 99 per cent. of the whole substance will pass into the chloroform. On separating this layer, and again agitating the aqueous liquid with an equal quantity of chloroform, 99 per cent. of the remaining substance will be dissolved, thus making the exhaustion practically complete. In the case of ether and amylic alcohol, the solubility of the solvent itself in the aqueous liquid is also an important consideration; for, as ether is soluble in about ten times its measure of water, on agitating together equal measures of ether and an aqueous liquid, it may be assumed that one-tenth of the ether will be dissolved, and will remain in the aqueous liquid together with its one-tenth share of the alkaloid or other substance to be extracted. On separating the ethereal layer, and again shaking the aqueous liquid with an equal measure of ether, it may be considered that nine-tenths of the previously dissolved ether and its alkaloid will be recovered in the immiscible solvent. On the other hand, the ethereal layer is not wholly free from water, which may be expected to take up certain substances not soluble in anhydrous ether; but practically such traces of impurity are removed on agitating the ether with a limited quantity of water. Similar considerations of solubility apply to treatments with chloroform, but with considerably less force owing to its slight solubility in water and *vice-versa;* and in the case of petroleum-ether and benzene they have no practical bearing, as these solvents are almost absolutely insoluble in aqueous liquids.

In making a proximate analysis by means of immiscible solvents, much of the success in practice depends on the care and skill with which the manipulation is conducted. The most convenient apparatus for effecting the treatment consists of a pear-shaped (fig. 1) or cylindrical (fig. 2) glass separator, furnished with a tap below and a stopper at the top. The tube below the tap should be ground obliquely so as to prevent loss of liquid by imperfect delivery. Supposing that it be desired to effect the separation of a substance from an aqueous liquid by agitation with ether, the former is introduced into the separator, of which it should not occupy more than one-third, acid or alkali added as may be desired, and next a volume of ether about equal to that of the aqueous liquid. The stopper is then

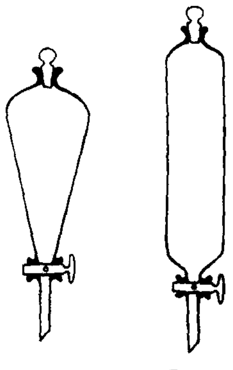


Fig. 1. Fig. 2.

inserted and the whole thoroughly shaken together for a minute or two, and then set aside. As a rule, the contents will readily separate into two well-defined layers, the lower of which is aqueous, and the upper ethereal. Sometimes separation into layers does not occur readily, the liquid remaining apparently homogeneous, forming an emulsion, or assuming a gelatinous consistency. In such cases, separation may sometimes be induced by thoroughly cooling the contents of the separator. In the case of ether, the separation may usually be effected by adding an additional quantity of ether and re-agitating, or, when the employment of a sufficient excess of ether is inconvenient or impracticable, the addition of a few drops of alcohol, followed by a gentle rotatory motion of the liquid, will almost invariably cause separation to occur promptly.

The tendency to form an obstinate emulsion is greatest when the aqueous liquid is alkaline, and is often very troublesome when chloroform, benzene, or petroleum-ether is substituted for ether. In such cases, the employment of a larger quantity of the solvent sometimes causes separation, but, when admissible, a better plan is the addition of ether. This answers very successfully for the isolation of strychnine, which is nearly insoluble in unmixed ether, but readily soluble in a mixture of equal measures of ether and chloroform. This solvent is heavier than water, and is capable of very extensive application.

Separation having taken place, the aqueous layer should be run off by the tap into another separator, where it can again be agitated with ether to insure the complete removal of the body to be dissolved therein. The ethereal liquid remaining in the first separator should be shaken with a fresh quantity of alkalised or acidulated water, which is then tapped off as before, and the remaining traces removed by treating the ether with a little pure water. This having in turn been run off to the last drop, the ethereal solution can next be removed by the tap, but a preferable plan is to pour it off from the mouth of the separator, taking care to avoid the draining of any drops of aqueous liquid from the sides of the glass.

When amylic alcohol, benzene, or petroleum ether is employed, the manipulation is the same as that just described; but when chloroform is used, or a mixture containing a considerable proportion of that solvent, the aqueous liquid forms the upper stratum, and the chloroformic solution can at once be removed by the tap.

When the volume of fluid treated with the immiscible solvent

is very small, the syringe pipette shown in fig. 3 may be conveniently substituted for a tapped separator. It is readily constructed by drawing out a test-tube, so as to form a narrow prolongation, the orifice of which should be turned up so as not to disturb the liquid in which it is immersed. A narrow test-tube fashioned into a handle at the upper part serves as a piston, a short length of india-rubber tubing uniting it to the outer tube, while allowing of easy movement both in a vertical and a horizontal direction.

Fig. 3.

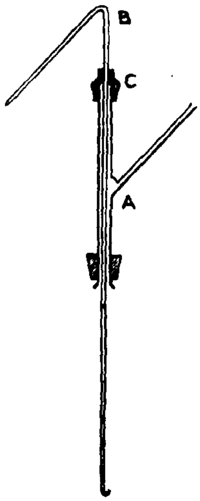


Fig. 4.

Another convenient form of separator, devised by W. Chattaway, is shown in fig. 4. It is practically a small wash-bottle fitting, which is adjusted to the tube or cylinder containing the layers of liquid it is desired to separate. It is so arranged that the exit-tube (B) can be adjusted in height by sliding it through the india-rubber collar C, so as to bring the turned-up end just above the junction of the two layers. On then blowing through the side-tube (A), the upper stratum is forced up the inner tube, and can be removed, almost to the last drop, without disturbing the lower layer.

The following table shows the behaviour of various classes of organic substances when shaken in acidulated or alkalised solution with immiscible solvents, such as ether, chloroform, amylic alcohol, benzene, and petroleum ether. It must not be supposed, however, that the immiscible solvents can be employed indifferently, as some of the bodies are readily removed by certain solvents, but are unaffected by others owing to their limited solubility therein. This is especially the case with the alkaloids and glucosides, and hence the table must merely be regarded as showing their general tendency, their special behaviour with the different solvents being deferred for fuller description later on.

Table showing the behaviour of Organic Substances with Immiscible Solvents.

<table>
<tr><td colspan="4">On agitating the substance with water, acidulated with sulphuric acid, and a suitable solvent immiscible therewith (such as ether, chloroform, amylic alcohol, benzene, or petroleum ether), the following distribution will occur:—</td></tr>
<tr><td colspan="2">The Immiscible Layer will contain hydrocarbons, oils, various acids, resins, colouring matters, phenols, glucosides, &c., which may be further separated by agitating the liquid with water containing caustic soda, when there will be obtained:—</td><td colspan="2">The Acidulated Aqueous Liquid will contain carbohydrates, soluble alkaloids and acids, organic bases, proteids, &c., which may be further separated by adding a moderate excess of soda, and again shaking with a suitable immiscible solvent, when there will be obtained:—</td></tr>
<tr>
<td>In the Immiscible Layer—
Solid Hydrocarbons; as paraffin, naphthalene, anthracene.
Liquid Hydrocarbons; as petroleum products, rosin-oil, benzene.
Essential Oils; as turpentine.
Nitro-compounds; as nitrobenzene.
Ethers and their Allies; as ether, chloroform, ethereal salts, nitroglycerin.
Fixed Oils, Fats, and Waxes.
Neutral Resins and Colouring Matters.
Chlorophyll.
Camphors; as laurel-camphor, borneol, menthol.
Alcohols insoluble or nearly insoluble in water; as amyl and cetyl alcohols, cholesterin.
Certain Glucosides, &c.; as saponin, digitalin, santonin.
Certain Weak Alkaloids; as caffeine, colchicine, narcotine, piperine, theobromine.</td>
<td>In the Alkaline Aqueous Liquid—
Fatty Acids; as stearic, oleic, valeric.
Various other Acids; as benzoic, salicylic, phthalic, meconic.
Acid Dyes and Colouring Matters; as picric and chrysophanic acids, alizarin, aurin, bilirubin.
Acid Resins; as colophony.
Phenoloids; as carbolic and cresylic acids, thymol, creosote.
Certain Glucosides, &c.; as santonin, cantharidin, picrotoxin.</td>
<td>In the Immiscible Layer—
Most Vegetable Alkaloids; as quinine, strychnine, aconitine, atropine, nicotine (cinchonine, morphine; the last two with difficulty).
Coal-Tar Bases; as aniline and its homologues (rosaniline), chrysotoluidine (pyridine), homologues of pyridine.</td>
<td>In the Alkaline Aqueous Liquid—
Carbohydrates; as sugars, gums, dextrin.
Soluble Alcohols; as methyl alcohol, ethyl alcohol, glycerin.
Soluble Acids; as acetic, oxalic, lactic, malic, tartaric, sulphophenic.
Certain Alkaloids and Organic Bases; as curarine, cytisine, narceine, urea, glycocine, solanine, and possibly cinchonine, morphine and pyridine.
Certain Colouring Matters; as indigo-products.
Proteids and their Allies; as albumin, casein, gelatin.</td>
</tr>
</table>

The foregoing table merely exhibits the *general* behaviour of the alkaloids and other plant-principles on agitating their solutions with immiscible solvents. G. Dragendorff, however, has elaborated the following scheme for systematic treatment by immiscible solvents. The statements are made on his authority, and in some cases (*e.g.*, the alleged removal of cinchonine from acid solutions by chloroform) are of questionable accuracy.

Extraction of Alkaloids and other Principles from Aqueous Liquids by Immiscible Solvents (after Dragendorff).

The liquid is warmed to about 40° or 50° C., rendered distinctly acid with dilute sulphuric acid, and agitated with an equal measure of petroleum ether, which is then separated.							
Petroleum Ether extracts from the *acidulated* liquid:— *Bases*— Piperine. *Non-Basic Principles*— Absinthin (incompletely). Capsicum (pungent principle). Hop Bitter (incompletely). Salicylic acid.	Aqueous Liquid is agitated at 40° or 50° C. with an equal measure of warm *benzene*, and separated.						
	Benzene extracts from the *acidulated* liquid:— *Bases*— Berberine (traces). Caffeine. Colchicine. Piperine (residual portion). *Non-Basic Principles*— Caryophyllin. Cascarillin. Cnicin. Colocynthin. Cubebin. Daphnin. Delphin. Digitalin. Elaterin. Ericolin. Gratiolin. Populin. Quassiin.	Aqueous Liquid is agitated with *chloroform*, and separated.					
		Chloroform extracts from the *acidulated* liquid:— *Bases*— Cinchonine (very doubtful). Colchicine. Geissospermine. Narceine. Papaverine. Quebrachine. Theobromine. *Non-Basic Principles*— Benzoic Acid. Convallamarin. Digitaleïn. Helleboreïn. Œsculin. Physalin. Picrotoxin. Saponin. Senegin. Syringin.	Aqueous Liquid is agitated once with *petroleum ether* to extract dissolved *chloroform*, separated, more *petroleum ether* added, then a moderate excess of *ammonia*, agitated and separated.				
			Petroleum Ether extracts from *ammoniacal* solution:— *Bases*— Aniline. Conine and methylconine. Conhydrine. Nicotine. Papaverine. Quinine. Sparteine. Trimethylamine. Bases of capsicum, pimento, and *Sarracea purpurea*, with *traces* of brucine, emetine, sabadilline, sabatrine, strychnine, veratrine, &c.	Aqueous Liquid is agitated with *benzene*, and separated.			
				Benzene extracts from the *ammoniacal* solution:— *Bases*— Atropine. Aconitine. Aspidospermine. Brucine. Codeine. Delphinine and Delphinoidine. Emetine. Gelsemine. Hyoscyamine. Narcotine. Pereirine. Physostigmine. Pilocarpine. Quinidine. Sabadilline. Sabatrine. Strychnine. Taxine. Thebaine. Veratrine, and a *trace* of cin-	Aqueous Liquid is agitated with *chloroform*, and separated.		
					Chloroform extracts from the *ammoniacal* solution:— *Bases*— Celandine bases. Cinchonine. Narceine. Nupharine. Papaverine, and *traces* of morphine; together with the bases soluble in benzene, which may have escaped extraction by that solvent.	Aqueous Liquid is agitated with *amylic alcohol* at 60° C., and separated.	
						Amylic Alcohol extracts from the *ammoniacal* solution:— *Bases*— Narceine (partly). Morphine. Solanine (solution gelatinizes on cooling). *Non-Basic Principles*— Salicin.	Aqueous Liquid (ammoniacal) retains:— *Bases*— Curarine. Narceine, and *traces* of berberine. *Non-Basic Principles*— Digitalin.

It is evident that the method of Dragendorff, set forth in the foregoing table, effects some very important differentiations; but for many purposes the process may be simplified with advantage. Thus, for instance, if the directions of Dragendorff be adhered to, the aqueous solution will be treated at least seven times (and possibly twice as many) with immiscible solvents before the extraction of morphine with amylic alcohol is attempted. As morphine is not wholly insoluble in the solvents previously used, small quantities, such as are generally met with in toxicological inquiries, are liable to escape detection. Again, agitation of the acidulated liquid with petroleum-ether removes but few active principles, though it is often useful for purifying the liquid from colouring matters, traces of resins, and fatty acids precipitated on acidulating, &c. The subsequent treatments with benzene may often be omitted, as the bodies thereby extracted are also dissolved by chloroform. They consist of glucosides and other neutral and feebly acid principles, with a few alkaloids of feeble basic character. The treatment with petroleum-ether in ammoniacal solution is chiefly of service for the isolation of the volatile bases (conine, nicotine, sparteine, &c.), and in their absence may often be advantageously omitted. In fact, the three extractions in ammoniacal solution by petroleum-ether, benzene, and chloroform may in many cases be replaced by treatment with chloroform alone, or a mixture of ether and chloroform, which last menstruum possesses the great advantage of separating readily from alkaline liquids.

The alkaloids and other principles having been separated into groups by Dragendorff's method, the various solutions may be carefully evaporated and the residues examined for the substances supposed to be present. The special tests suitable for this purpose are described in the sequel.

A valuable method of extracting alkaloids is that of Claus, who employed it especially for the estimation of caffeine in tea, and of quinine in bark, but it is capable of many other applications. In assaying tea, the powdered leaves are dried and extracted with ether, the solvent dissolved off, and the residue extracted with sulphuric acid. The acid liquid is filtered, mixed with excess of ignited magnesia, evaporated to dryness at 100°, and the residue pulverised and extracted with boiling ether. For the extraction of quinine, the powdered bark is exhausted by water acidulated with sulphuric acid, the solution evaporated with excess of magnesia, and the dry residue exhausted with ether.

A. Loesch (*Year-Book Pharm.*, 1880, page 60) treats the crude and concentrated alkaloidal solution obtained by suitable

means with three measures of a cold saturated solution of alum, and then adds a slight excess of ammonia. The liquid containing the precipitate is evaporated to dryness at 100°, and the powdered residue exhausted with a suitable solvent. On evaporating the solution, the alkaloid is obtained in colourless ash-free crystals. Loesch quotes the following results, as compared with those yielded by Claus' magnesia method, and titration by Mayer's solution (page 140):—

Material Employed.		Percentage of Alkaloid Extracted.		
		Claus.	Mayer.	Loesch.
Cinchona bark (yellow), .	quinine, . . .	3·175	2·570	3·250
	cinchonidine, . .	0·250	0·175	0·285
Cinchona bark (red), .	quinine, . . .	1·195	1·005	1·235
	cinchonidine, . .	0·500	0·395	0·525
Cinchona bark (brown), .	quinine, . . .	0·950	0·800	0·975
	cinchonidine, . .	2·975	2·300	3·075
Hyoscyamus leaves, ...		0·145	0·074	0·175
Hyoscyamus seeds, ...		0·225	0·100	0·285
Belladonna leaves, ...		0·197	0·090	0·235
Belladonna roots, ...		0·325	0·225	0·375
Ipecacuanha root, ...		0·800	0·475	0·875
Aconite leaves, ...		0·395	0·220	0·425

J. U. Lloyd (*Pharm. Jour.*, [3], xxi. 1144) recommends for the assay of alkaloidal extracts the addition of ferric chloride solution, and then sufficient solid sodium bicarbonate to convert the whole into a paste. This is treated in a porcelain mortar with chloroform, which is poured off and the treatment twice repeated. The alkaloid is then shaken out from its chloroform solution with dilute acid, the latter liquid agitated with ether to remove chlorophyll, &c., and the alkaloid again liberated and extracted by a suitable solvent.

If a *volatile alkaloid* be present it will generally be evident by its odour, at whatever point of the operation it is liberated from its combination by an alkali. Should its presence be thus detected or suspected, it may be conveniently isolated by adding excess of lime or baryta, and distilling the liquid. The alkaloid can be fixed in the distillate by adding a slight excess of hydrochloric acid, and after concentrating the liquid to a small bulk may be liberated by adding a large excess of caustic alkali, and extracted by agitation with ether (compare page 170).

The alkaloids having been obtained in a state of approximate purity by one of the foregoing methods, they may be further treated according to one of the following principles, which may be applied in many cases at an early stage of the process.

a. Fatty and resinous matters and *chlorophyll* may be removed by agitating the acidulated solution of the alkaloid with petroleum spirit or ether. (Piperine and some glucosides are also extracted.)

b. Colouring matters may be removed by agitating the solution with a small quantity of animal charcoal,[1] but this agent must be used very sparingly, or the alkaloid may be wholly removed from solution. The alkaloid thus taken up may be recovered by boiling the charcoal with alcohol. The absorption of alkaloids by charcoal has been employed for their removal from beer and similar liquids.

c. Many *colouring matters*, and *tannic* and various other *organic acids*, may be removed by treating the neutral solution with lead acetate, and filtering.

d. From sugars, gums, salts, and *extractive matters generally*, the great majority of the alkaloids can be separated by adding ammonia, and agitating the solution with chloroform or a mixture of chloroform and ether. On separating the chloroform from the aqueous liquid, which retains the sugar, gum and salts, and agitating it with dilute sulphuric acid, the alkaloid passes into the acid liquid, while colouring matters, fats, resins, &c., remain in the chloroform.

e. The alkaloid may be precipitated with iodised potassium iodide, Mayer's reagent, auric chloride, or platinic chloride, the precipitate being purified by recrystallisation from water, alcohol, or other suitable solvent, and recovered by appropriate means.

By a judicious application of the above principles it is generally an easy matter to isolate alkaloids in a nearly pure condition, or at any rate in such a state as to allow of the special tests being successfully applied. H. B. Parsons' systematic scheme for the proximate analysis of plants detailed in Vol. I. page 365 *et seq.* will also be of service in the isolation of alkaloids.

A good example of the separation of alkaloids from woody fibre and tannin matters is furnished by the processes for the assay of cinchona barks; the separation of alkaloids from resinous, gummy, and colouring matters is exemplified in the methods for the assay of opium; while the isolation of strychnine in toxicological investigations is a good illustration of the methods employed for the separation of alkaloids from albuminous, starchy, and fatty matters. The last method is of tolerably general applicability in toxicological investigations, provided that it be remembered that (1) many alkaloids are far less stable than strychnine, and hence are apt to be

[1] Made by boiling bone-charcoal with hydrochloric acid, filtering, and thoroughly washing the insoluble residue of carbon.

destroyed if the solutions are evaporated at too high a temperature (compare aconitine); (2) that certain alkaloids are extracted by chloroform and amylic alcohol even from their acidulated solutions; (3) that curarine, cytisine, morphine, and solanine are nearly or quite insoluble in ether or chloroform, and hence cannot be certainly extracted by agitating their alkaline solutions with either of these solvents; (4) that, whenever possible, the chemical tests for the isolated alkaloids should be supplemented by physiological tests; and (5) that, during the process of putrefaction, certain cadaveric alkaloids ("ptomaines") are liable to be formed which simulate some of the reactions of the vegetable bases, but are distinguishable from them by careful examination.

CONSTITUTION AND SYNTHESIS OF ALKALOIDS.[1]

Some of the alkaloids of widely different properties present a curious analogy in their formulæ. This resemblance in empirical composition is merely accidental, as is proved in many cases by the products of decomposition. The following are some of the most striking cases of the kind:—

Atropine,	$C_{17}H_{23}NO_3$	Colchicine,	$C_{22}H_{25}NO_6$
Cocaine,	$C_{17}H_{21}NO_4$	Narcotine,	$C_{22}H_{23}NO_7$
Morphine,	$C_{17}H_{19}NO_3$	Quinine,	$C_{20}H_{24}N_2O_2$
Piperine,	$C_{17}H_{19}NO_3$	Strychnine,	$C_{21}H_{21}N_2O_2$
Pseudaconitine,	$C_{36}H_{49}NO_{12}$	Picraconitine,	$C_{31}H_{45}NO_{11}$
Veratrine,	$C_{37}H_{53}NO_{11}$	Cevadine,	$C_{32}H_{49}NO_9$

The foregoing coincidences have little theoretical value, as no real insight into the constitution of the alkaloids can be obtained by a consideration of mere empirical formulæ.

Some of the most important advances in the synthetical production of alkaloids have been due to a study of the products obtained by hydrogenating pyridine and its allies, assisted by a better recognition of the relationship of these bases to each other, and to benzene and other hydrocarbons. Thus, the bases pyridine, quinoline, and acridine form a series related to each other exactly in the same way as the hydrocarbons benzene, naphthalene, and anthracene are related (page 39). The stability

[1] Much of the information contained in the test is derived from a lecture by S. P. Sadtler (*Pharm. Jour.*, [3], xx. 544), and from the address of A. B. Prescott to the Chemical Section of the American Association for the Advancement of Science (*Pharm. Jour.*, [3], xviii. 520, 541).

and the behaviour towards reagents of the corresponding derivatives of benzene and pyridine are exactly analogous, as also is their behaviour on reduction. Just as from benzene hexahydrobenzene can be obtained, so from pyridine hexahydropyridine may be prepared, but far more readily. Similarly from naphthalene and quinoline, tetrahydro-additive-products are obtainable, while from anthracene and acridine, respectively, dihydro-anthracene and dihydro-acridine (page 125) have been obtained.

Of these hydro-addition-products, one of the best-studied is hexahydropyridine, $C_5H_{11}N$, which is identical with the volatile base *piperidine*, obtainable from *piperine*, $C_{18}H_{18}NO_3$, the alkaloid of pepper, by distillation with alkali, by the action of reducing agents on pyridine, C_5H_5N, or by heating the hydrochloride of pentamethylene-diamine, $C_5H_{10}(NH_2)_2$ (page 106).

Another natural plant-base which has been prepared synthetically, and the nature and derivation of which are clearly understood, is *conine*, $C_8H_{17}N$, the volatile poisonous alkaloid of hemlock. Conine is the dextro-rotatory variety of α-normal-propyl-piperidine, $C_5H_{10}(C_3H_7)N$. To prepare it synthetically, pyridine is first converted into α-allyl-piperidine, $C_5H_4N(C_3H_5)$, which is then reduced in alcoholic solution by means of sodium. In this reaction, the chief product is the optically inactive α-normal-propyl-piperidine, which is separated by crystallisation of the tartrate into ordinary *conine* (dextro-conine), and a lævo-rotatory conine which closely resembles the other modification.[1]

The optically inactive conine can also be prepared from conyrine, or α-normal-propyl-piperidine, by treatment with hydriodic acid, or from *conhydrine*, $C_{18}H_{17}NO$, an oxy-derivative occurring with conine in hemlock. A. W. Hofmann has described three isomeric bases, called α-, β-, and γ-coniceïne, having the formula $C_8H_{15}N$, and hence differing from conine by H_2. These bases have a mousy smell like conine, and the α and γ modifications are more powerful poisons than conine itself (see page 174).

Nicotine, $C_{10}H_{14}N_2$, the volatile alkaloid of tobacco, is another base related to pyridine, and the synthesis of which has been at least partially effected. Thus the two known dipyridyls, $C_{10}H_8N_2$, are the *para*- and *meta*-modifications. On reduction, these yield the corresponding hexahydro-dipyridyls, $C_{10}H_8(H_6)N_2$, which are bases called respectively isonicotine

[1] These two bases bear the same relation to each other, and to the inactive modification that dextro- and lævo-tartaric acids bear to racemic acid. Exactly analogous ethyl-piperidines have been prepared.

and nicotidine, isomeric with nicotine. On treatment with oxidising agents nicotine yields nicotinic or β-pyridine-carboxylic acid, $C_5H_4N.COOH$,[1] a reaction which shows the close relationship of nicotine to the homologues of pyridine.

Atropine, $C_{17}H_{23}NO_3$, is another plant-base of which the relationship to pyridine has been very clearly established. Thus when boiled with alkalies atropine is hydrolysed into tropine, $C_8H_{15}NO$, and tropic acid, $C_9H_{10}O_3$; while *hyoscine*, base isomeric with atropine, is similarly split up into tropic acid and pseudotropine. Tropine has the constitution of a hydroxyethyl-methyl-tetrahydropyridine, $C_5H_7(C_2H_4OH)(CH_3)N$. On boiling with acids it loses the elements of water and is converted into tropidine, a liquid base with a conine-like odour, and has been synthesised by Ladenburg by introducing a methyl and hydroxyethyl atom into tetrahydropyridine. Tropic acid and tropine reunite to form atropine when their solutions in dilute hydrochloric acid are mixed and evaporated. By substituting other aromatic acids for tropic acid a great variety of bodies can be obtained, which are generically termed tropeïnes, and one of which, the mandelic acid derivative or homatropine, has proved physiologically important.

The *pyridine-carboxylic acids* (page 110), and their analogues and derivatives, have shown some unexpected relationships to the natural plant-bases. The β-pyridine-carboxylic acid (nicotinic acid) results from the oxidation of nicotine and pilocarpine. Cinchomeronic acid (α-pyridine-dicarboxylic acid) is produced by the oxidation of cinchonine, cinchonidine, and quinine. One of the pyridine-tricarboxylic acids is produced by the oxidation of the cinchona-bases and papaverine with permanganate, while a second results from the oxidation of berberine by nitric acid. The pyridine-carboxylic acids also furnish additive-products analogous to the betaïne of beet-juice, and closely related to the natural alkaloids. The synthetically produced betaïne of nicotinic or β-pyridine-carboxylie acid has been shown to be identical with the alkaloid of *Trigonella fœnugræcum*, while the betaïne of cinchmoeronic acid is identical with apophyllic acid, obtained by the oxidation of cotarnine (see narcotine).

The pyridyl-residue, C_5H_4N, is capable of replacing an atom of hydrogen in the molecule of certain acids, the compounds having the same relation to the salts of pyridine that (*e.g.*) aniline acetate has to acetanilide. *Pilocarpidine*, which occurs with pilo-

[1] The same pyridine-carboxylic acid may be obtained by the action of ammonia on coumalinic acid, produced by the action of sulphuric acid on malic acid.

carpine in japorandi leaves, is a β-pyridine-α-dimethylamidopropionic acid, having probably the constitution:— $N(CH_3)_2.C(CH_3)C_5H_4N.COOH$. It has been prepared synthetically, and from it, by the action of methyl iodide and caustic alkali, followed by silver permanganate, *pilocarpine* itself has been obtained, and may be regarded as having the following constitution:—

$$\begin{array}{l} C_5H_4N.C(CH_3)N(CH_3)_3 \\ \qquad\quad | \qquad\;\; | \\ \qquad\;\; CO - O \end{array}$$

The action of ammonia upon certain acids found in the vegetable kingdom has been found to produce bodies related to pyridine. Thus comanic acid, $C_6H_4O_4$, derived from meconic acid, is changed by ammonia into an oxypicolinic acid, while comenic acid, $C_6H_4O_5$, from the same source, yields a dioxypicolinic acid, comenamic acid, $C_6H_5NO_4$. Similarly chelidonic acid, $C_7H_4O_6$, which accompanies the alkaloids *chelidonine* and *sanguinarine* in *Chelidonium majus*, yields an oxypyridinecarboxylic acid on treatment with ammonia.

Colchicine is another alkaloid the constitution of which is fairly well known. From its reactions and the products of its decomposition, it is evidently the methyl-ester of acetyl-trimethylcolchicinic acid, $(O.CH_3)_3.C_{15}H_9(NH.C_2H_3O).CO.OCH_3$.

Ecgonine has the constitution of a methyltetrahydropyridylhydroxypropionic acid, $C_5H_6MeN.CH(OH).CH_2.COOH$. It results, together with methyl alcohol and benzoic acid, from the decomposition of cocaine by alkalies. *Cocaine* may be made synthetically by heating ecgonine with benzoic anhydride and methyl iodide, and has the following constitution:—

$$C_5H_6(CH_3)N.CH(O.C_7H_5O).CH_2.COO(CH_3).$$

A series of analogous artificial alkaloids have been prepared by combining ecgonine with other acids besides benzoic.

The constitution of the *aconite bases* is partially known, for they split under the influence of hydrolysing agents into simpler bases and acids of the aromatic series; aconitine, picraconitine, and japaconitine yielding benzoic acid, $C_6H_5.COOH$, while pseudaconitine gives veratric or dimethyl-protocatechuic acid, $C_6H_3(OCH_3)_2.COOH$. The pseudaconine, $C_{27}H_{41}NO_9$, simultaneously produced in the last case, forms a diacetyl-derivative, and hence probably contains two hydroxyl groups.

Veratric acid is also produced, together with verine, $C_{28}H_{45}NO_8$, by the saponification of *veratrine*, while the accompanying base, *cevadine*, $C_{32}H_{49}NO_9$, is converted on hydrolysis into cevine, $C_{27}H_{43}NO_8$, and methyl-crotonic acid, $C_3H_4(CH_3).COOH$.

Sinapine, $C_{16}H_{23}NO_5$, an alkaloid the thiocyanate of which exists in white mustard seed, is split by boiling with baryta-water into sinapic acid, $C_{11}H_{12}O_5$, and *choline*, $C_{15}H_{15}NO_2$, a base which is contained in bile and other animal products, as well as in hops and certain other plants. Choline has itself been obtained synthetically, and has the constitution of a hydroxyethyl-trimethyl-ammonium hydroxide, $(C_2H_4OH)(CH_3)_3N.OH$.

Theobromine, $C_5H_2(CH_3)_2N_4O_2$, the alkaloid of cocoa, and *caffeine*, $C_5H(CH_3)_3N_4O_2$, the alkaloid of tea and coffee, are respectively the dimethyl and trimethyl derivatives of xanthine, $C_5H_4N_4O_2$, a body occasionally occurring in urinary calculi and produced by the action of nitrous acid on guanine, $C_5H_5N_5O$ (contained in guano), or by treating uric acid, $C_5H_4N_4O_3$, with sodium amalgam.

Lupinine, an alkaloid found in seeds of *Lupinus luteus*, has the formula $C_{21}H_{38}N_2(OH)_2$. *Arginine*, $C_6H_{14}N_4O_2$, from the same source (page 178) yields urea when boiled with baryta water.

The manner in which the oxygen of the natural alkaloids exists is in most cases but little understood. *Morphine*, $C_{17}H_{19}NO_3$, appears, however, to have a phenolic character, and contains two hydroxyl atoms replaceable by acetyl or benzoyl. *Codeine* is a substituted morphine in which one of the hydroxyl atoms is replaced by methoxyl, OCH_3, and has been obtained synthetically by heating morphine with methyl iodide. By similar means the second hydroxyl atom can be replaced by methoxyl with formation of *methocodeine*. *Thebaine* differs from methocodeine by two atoms of hydrogen, thus :—

Morphine, ...	$C_{17}H_{17}NO\begin{cases}OH\\OH\end{cases}$
Codeine, ...	$C_{17}H_{17}NO\begin{cases}OH\\O(CH_3)\end{cases}$
Methocodeine, ...	$C_{17}H_{17}NO\begin{cases}O(CH_3)\\O(CH_3)\end{cases}$
Thebaine, ...	$C_{17}H_{15}NO\begin{cases}O(CH_3)\\O(CH_3)\end{cases}$

When distilled with zinc-dust, morphine yields phenanthrene, $C_{14}H_{10}$, and pyridine, C_5H_5N.

Narcotine, $C_{22}H_{27}NO_7$, is saponified under certain conditions with formation of meconin, $C_{10}H_{10}O_4$, and cotarnine, $C_{12}H_{13}NO_3$; and the latter body when treated with bromine yields dibrompyridine, $C_5H_3Br_2N$. Cotarnine probably contains its oxygen in the forms of $CO.OCH_3$ and OCH_3. On oxida-

tion it yields apophyllic acid, a body which, when heated under pressure with hydrochloric acid, behaves like the methylester of cinchomeronic acid :—

$$C_5H_3N\begin{cases}CO.OH\\CO.O(CH_3)\end{cases} + HCl = CH_3Cl + C_5H_3N\begin{cases}CO.OH\\CO.OH\end{cases}$$
Apophyllic acid. Methyl chloride. Cinchomeronic acid.

Papaverine, $C_{20}H_{21}NO_4$, is another opium base, the constitution of which is probably :—$(OCH_3)_2C_9H_4N.CH_2.C_6H_3(OCH_3)_2$.

Brucine, $C_{23}H_{20}N_2O_4$, when fused with caustic potash yields homologues of pyridine, while *strychnine*, $C_{21}H_{22}N_2O_2$, yields quinoline and indole, C_8H_7N.

Quinine, $C_{20}H_{24}N_2O$, when fused with caustic potash yields methoxy-quinoline, $C_9H_6(O.CH_3)N$. When subjected to careful oxidation with permanganate or weak chromic acid mixture it at first yields formic acid, CH_2O_2, and a weak base called quitenine, $C_{19}H_{22}N_2O_4$. Further oxidation produces three bases, to which Skraup attributes the formulæ $C_{13}H_{16}NO_2$, $C_9H_{17}NO_2$, and C_9H_7NO. The first of these has been little studied, the second has been named cincholeupone, $C_9H_{17}NO_2$, and the third appears to be identical with kynurine, a base obtained by heating kynurenic acid, a constituent of dog's urine. Besides these bases there are produced cincholeuponic acid, $C_8H_{13}NO_4$;[1] quininic acid, $C_9H_5(O.CH_3)N.COOH$; then a pyridine-tricarboxylic acid, $C_5H_2N(CO.OH)_3$; and finally the pyridine-dicarboxylic acid known as cinchomeronic acid, $C_5H_3N(CO.OH)_2$. *Quinidine* and *quinicine* yield the same products as quinine. *Cinchonine*, $C_{19}H_{22}N_2O$, when similarly subjected to limited oxidation, yields formic acid and cinchotenine, $C_{18}H_{20}N_2O_3$, as first products; the latter by further treatment yields cincholeupone, $C_9H_{17}NO_2$, and this oxidises to cinchoninic acid, $C_{10}H_7NO_2$, and cincholeuponic acid, $C_8H_{13}NO_4$; the final products being cinchonic acid, $C_5H_4N.COOH$ (which is a pyridine-carboxylic acid), and cinchomeronic acid (see above). *Cinchonidine* and *cinchonicine* appear to yield the same products.

The conclusion derivable from the researches on the constitution of the cinchona bases is that both quinine and cinchonine are derivatives of a hydro-diquinoline, of which probably only one side is hydrogenated. The same unreduced quinoline-residue is common to both alkaloids, with the difference that, while in cinchonine

[1] Cincholeuponic acid probably has the constitution of a methyl-piperidine-dicarboxylic acid :—

$$HN\begin{cases}.CH_2.CH_2.CH_2.\\.C(CH_3)(COOH).CH(COOH).\end{cases}$$

the residue is quinoline itself, in quinine it is a methoxy-quinoline. The following formulæ illustrate these deductions:—

Quinoline, . .	C_9H_7N
Hydroxyquinoline, .	$C_9H_6(OH)N$
Tetrahydroquinoline,	$C_9H_{10}N.H$
Diquinoline, . .	$C_9H_7N.C_9H_7N$
Diquinolyline, .	$C_9H_{10}N.C_9H_{10}N$
Cinchonine, . .	$C_9H_7N.C_9H_{11}(OH)N.CH_3$
Quinine, . .	$C_9H_6(O.CH_3)N.C_9H_{11}(OH)N.CH_3$

Other of the cinchona bases which are known to contain hydroxyl groups are *quinidine*, $C_{20}H_{23}N_2O(OH)$, and *cupreine*, $C_{19}H_{20}N_2(OH)_2$. The latter alkaloid, which is found in Cuprea and Remijia barks, has recently been converted into quinine by heating it to 100°, under pressure, with metallic sodium and a solution of methyl chloride in methyl alcohol (Grimaux and Arnold, *Comp. Rend.*, cxii. 774).

Although the knowledge of the constitution of the cinchona bases is not yet sufficiently perfect to allow of their formation from pyridine or quinoline, it is interesting to note that two distinct basic substances isomeric with quinine have been prepared synthetically. One of these, discovered by C. A. Kohn (*Jour. Soc. Chem. Ind.*, viii. 959), has the constitution of an α-1′-hydroxy-hydro-ethylene-quinoline,

$$C_9H_{10}(OH)N.C_2H_4.N.C_9H_{10}(OH).$$

It was obtained by the action of one molecule of ethylene dibromide on two molecules of α-1′-hydroxyhydroquinoline, obtained by reducing hydroxy-quinoline by tin and hydrochloric acid. It is a weak base, forming small glittering prisms which melt at 233°, and are readily soluble in chloroform and benzene, with difficulty in hot alcohol, and insoluble in water. It has weak antipyretic characters.

The other synthetical isomer of quinine has been prepared by Wallach and Otto (*Annalen*, ccliii. 251) by the reaction of β-naphthylamine on pinol nitrosochloride:—

$$C_{10}H_7.NH_2 + C_{10}H_{16}O.NOCl = HCl + C_{20}H_{24}N_2O_2.$$

The product is a basic crystalline substance, melting at 194°–195°, insoluble in water, slightly soluble in hot alcohol, and readily soluble in ether. The solutions, both of the base and its salts, are strongly fluorescent.

Besides the natural plant-bases, a number of bases have been synthetically prepared which have every claim of analogy and

character to be ranked with the alkaloids. As instances of these may be mentioned *antipyrine*, $C_{11}H_{12}N_2O$ (page 32), *thalline*, $C_{10}H_{13}NO$ (page 120), and *furfurine*, $C_{15}H_{12}N_2O_3$.

V. Meyer has suggested that the formation of the bases and other nitrogenised constituents of plants may be due in some cases to the action of hydroxylamine on aldehydic bodies.

It is a curious fact that while the plant-bases and other natural products not unfrequently contain one or more methyl-groups, the ethyl-radical is not met with.

VOLATILE BASES OF VEGETABLE ORIGIN.

Certain plants contain bases which differ from the ordinary vegetable alkaloids, in being volatile, liquid at ordinary or only slightly raised temperatures, and in containing no oxygen. While resembling each other in the above respects, the volatile bases present little further resemblance.

The volatile alkaloids are not numerous, being limited to the following bodies, and a few others which have been but imperfectly investigated.

a. *Methylamine* and *Trimethylamine*, already described (pages 9, 12).
b. *Conine* and the associated alkaloids of hemlock.
c. *Lupinine* and certain other alkaloids of lupines.
d. *Nicotine*, the volatile alkaloid of tobacco.
e. *Piturine*, the volatile alkaloid of pituri.
f. *Lobeline*, the alkaloid of lobelia.
g. *Sparteine*, the alkaloid contained in broom.
h. *Spigeline*, an alkaloid in *Spigelia Marylandica*.

Piperidine, a volatile alkaloid said to exist naturally in pepper as a decomposition-product of piperine, has already been described (page 106).

For the *estimation* of volatile alkaloids (*e.g.*, conine in hemlock, and nicotine in tobacco), A. Loesch (*Jour. Amer. Chem. Soc.*) recommends that a weighed quantity of the substance should be boiled in water acidulated with hydrochloric acid, the residue pressed and washed with water. The solution and washings are evaporated to one-fourth, and then distilled with slaked lime (using a good condenser). When the liquid passing over is no longer alkaline to litmus, the distillate is exactly neutralised with sulphuric acid, evaporated to dryness at 100°, and the powdered residue exhausted with rectified spirit, which leaves the ammonium

sulphate undissolved, while the sulphate of conine (and other alkaloids) pass into the solution. The filtered liquid is evaporated to dryness and the residue skaken three times with caustic potash solution and ether, the ethereal liquid separated and shaken with a known volume of standard sulphuric acid, the ether distilled off or separated, and the excess of sulphuric acid determined by titration. By this process, Loesch found 5·25 per cent. of nicotine in tobacco leaves, and 0·06 per cent. of conine in the common hemlock plant.

Conine.[1] Coniine. Conia. Conicine.

$$C_8H_{17}N\ ;\ C_5H_{10}(C_3H_7)N\ ;\ \text{or}\ CH_2\left\{\begin{matrix}CH_2.CH(C_3H_7)\\CH_2.CH_2\end{matrix}\right\}NH$$

This base has the constitution of an α-normal-propyl-piperidine (see page 164).

Conine is the characteristic poisonous alkaloid of hemlock, *Conium maculatum*. It occurs in all parts of the plant, in combination with organic acids, and in association with the following allied bases :—

Base.	Formula.	Melting-Point, °C.	Boiling-Point, °C.	Specific Gravity.
Ethyl-piperidine, .	$C_7H_{15}N$; or $C_5H_9(C_2H_5)NH$	...	142–145	$\left\{\frac{0}{x}\right.=0·8674$
Conine (Normal-propyl-piperidine),	$C_8H_{17}N$; *or* $C_5H_9(C_3H_7)NH$	−2·5	167–170	$\left\{\frac{0}{x}\right.=0·8625$
Methyl-conine, .	$C_9H_{19}N$; or $C_5H_9(C_3H_7)N(CH_3)$	...	...	$\left\{\frac{12·5}{x}\right.=0·846$
Conhydrine, . .	$C_8H_{17}NO$; or $C_5H_9(CHOH.CH_2.CH_3)NH$	120·6	240 (225 at 720 mm.)	...
Pseudo-conhydrine,	$C_8H_{17}NO$; or $C_5H_9(CH_3.CH_2OH.CH)NH$	100–102	229–231	...

Conine is an oily liquid, having a peculiar repulsive odour,

[1] Conine has been prepared synthetically by the reducing action of sodium on a boiling alcoholic solution of allyl-pyridine, $C_5H_4(C_3H_5)N$, itself obtained from α-picoline and paraldehyde. The artificial base thus prepared *is identical in all its properties with the natural alkaloid, except that it is* optically inactive. But on introducing a crystal of the bitartrate of the natural alkaloid into a very concentrated solution of the bitartrate of the inactive bases, a gradual separation of the bitartrate of active conine occurs, the free base from which exhibits the same optical activity as natural conine. The mother-liquid contains a lævo-rotatory isomeric base (Ladenburg, *Ber.*, xix. 2578).

suggesting that of a long-used and foul tobacco-pipe. When diluted with water, conine has a peculiar and characteristic "mousy" odour, perceptible in highly dilute solutions. A few drops of an aqueous solution containing only 1–50,000 of the alkaloid, if enclosed for a short time in a small test-tube, is stated by Wormley to impart a marked mousy odour to the contained air.

Conine may be distilled without change in an atmosphere of hydrogen, but undergoes slight decomposition at high temperatures in presence of air. It distils readily with vapour of water or alcohol, and volatilises sensibly at ordinary temperatures.

Conine is optically active, its specific rotation being + 13°·8 for the sodium ray.

Conine forms an unstable compound with 25 per cent. of water, the water being expelled by heating. Conine is soluble in about 90 parts of cold water, and is readily dissolved by alcohol, acetone, amylic alcohol, ether, chloroform, petroleum ether, and benzene. The alkaloid is removed with tolerable facility from its aqueous or alkaline solutions by agitation with either of the last five solvents, and may be recovered therefrom by shaking the resultant solution with dilute acid.

Conine dissolves sulphur, but not phosphorus nor calcium chloride.

Conine is colourless when freshly prepared, but becomes yellow and ultimately resinoid by keeping.[1] It is a strong base, the aqueous solution being powerfully alkaline in reaction, and neutralising acids perfectly. The salts are colourless and odourless, but the peculiar odour of the free base is immediately developed on adding a fixed alkali in excess.

If a beaker moistened with fuming hydrochloric acid be inverted over a watch-glass containing a drop of free conine, white fumes will be produced, and the alkaloid will be converted after a time into a *crystalline hydrochloride*, $C_8H_{17}N,HCl$. (Nicotine gives an amorphous hydrochloride.) The hydrochloride is also obtained as a brilliant crystalline mass by dissolving conine in anhydrous ether, and passing dry hydrochloric acid gas through the solution. The salt is very soluble in water and alcohol, but insoluble in ether. It can be heated to 90° C. without decomposition or loss of weight. It melts at 218°.

The *hydriodide* of conine is anhydrous. It can only be obtained crystalline by the use of pure hydriodic acid free from any trace of iron. By slow evaporation the salt is obtainable in large flat needles, which sublime when gently heated *in vacuo*.

[1] According to Schorm, pure conine does not undergo any change by exposure to light (*Pharm. Jour.*, [3], xii. 363).

On adding a large excess of strong hydrochloric acid to conine, a pale red tint is produced, which gradually deepens in colour. Nitric acid acts similarly. Sulphuric acid produces no immediate change with conine, but the mixture gradually becomes purple-red, and then olive-green.

On exposing a drop of conine to the vapours of bromine (avoiding excess), it becomes rapidly converted into a mass of white crystals. This behaviour is regarded by Watts as a proof of the purity of the alkaloid.

By the treatment of conine with chromic acid mixture, normal butyric acid is produced. The reaction may be employed as a test for conine, as butyric acid has a highly characteristic odour, and can be readily distilled off and further examined. Butyric acid also results from the oxidation of conine by bromine-water or nitric acid, while permanganate converts it into picolinic acid.

On distillation of conine hydrochloride with zinc-dust, or the free base with zinc chloride, hydrogen is evolved and α-propyl-pyridine or conyrine, $C_5H_4(C_3H_7)N$, formed. This base boils at 166°–168°, and is reconverted into conine on treatment with hydriodic acid. (By prolonged treatment with hydriodic acid conine is converted into ammonia and octane, C_8H_{18}.)

Mercuric chloride produces with conine a white amorphous precipitate, readily soluble in hydrochloric or acetic acid. (Nicotine gives a crystalline precipitate.) With potassio-mercuric iodide, conine gives a voluminous curdy precipitate. Silver nitrate gives a brown precipitate of argentic oxide with free conine, the colour afterwards changing to black. (Nicotine gives a white precipitate with silver nitrate, turning dark on exposure to light.) *Conine chloroplatinate* is a readily soluble salt.

Conine gives a yellow precipitate with phosphomolybdic acid, and an orange precipitate with potassio-iodide of bismuth.

Picric acid does not precipitate conine from solutions containing less than 1 per 1000 of the alkaloid, but nicotine is precipitated from solutions fifty times more dilute.

Conine is said to coagulate albumin, thus differing from nicotine.

If conine be dropped into a solution of alloxan, an intense purple-red coloration is gradually produced, and white needles separate which dissolve with purple colour in cold potash solution.

The *alkaloids* occurring with conine in hemlock and its preparations are precipitated by Mayer's reagent, picric acid, and iodine from solutions considerably more dilute than those from which conine itself is thrown down.

CONHYDRINE has the probable constitution of a piperidyl-

ethylalkine, $C_5H_9(CHOH.CH_2.CH_3)NH$. It presents a close resemblance to tropine, $C_8H_{15}NO$, both in composition and chemical behaviour, a fact which suggested to A. W. Hofmann the probability that it was the product of the hydrolysis of a base allied to atropine. From the alkaline liquid left after the distillation of conine and conhydrine, Hofmann obtained, by acidulation and extraction with ether, caffeic acid, $C_9H_8O_4$, a body having the constitution of a dihydroxy-cinnamic acid.

Conhydrine may be separated from commercial conine, in which it is not unfrequently present, by cooling the liquid down to 5° C., filtering through glass wool, and washing the separated crystals of conhydrine with petroleum ether, in which it is but sparingly soluble. Pseudoconhydrine is a base isomeric with conhydrine, but probably containing hydroxy-isopropyl (Ladenburg, *Ber.*, xxiv. 1671). Conhydrine forms colourless glittering crystals, moderately soluble in water, but very soluble in alcohol and ether. It does not react with nitrous acid, has an alkaline reaction, and is a feeble narcotic poison. According to Wertheim, hemlock contains only 5 to 6 parts of conhydrine for every 100 of conine.

CONICEÏNES, $C_8H_{15}N$. These bases were obtained by A. W. Hofmann by the action of oxidising agents on conine, or of dehydrating agents on conhydrine. When molecular proportions of conine hydrobromide and bromine are mixed, the bromo-derivative, $C_8H_{17}N.HBr.Br_2$, is obtained. By the regulated action of caustic soda this yields $C_8H_{15}NBr$, which by treatment with sulphuric acid is decomposed into hydrobromic acid and *α-coniceïne*, which is a colourless liquid of ·893 specific gravity at 15°, boiling at 158°, and slightly soluble in water. In odour it closely resembles conine, but is said to be five or six times as poisonous! It is a tertiary base of strong alkaline reaction, and forms crystallisable salts. The *picrate* forms yellow needles melting at 225°, nearly insoluble in cold water, and very slightly soluble in alcohol. α-coniceïne is partially reduced to conine by heating under pressure with fuming hydriodic acid and phosphorus. *γ-coniceïne* is obtained by decomposing the bromo-derivative $C_8H_{15}NBr$ by an alkali. It is a colourless liquid lighter than water, boiling at 173°, distilling with steam, and said to be twelve times as poisonous as conine! It is only slightly soluble in water, but the solution is strongly alkaline. γ-coniceïne is a secondary base (pages 1, 7) yielding crystalline, volatile salts with acids, and a characteristic double salt with stannic chloride, $B_2H_2SnCl_6$, which forms large crystals. *β-coniceïne* is obtained together with α-coniceïne by the action of phosphoric anhydride or fuming hydrochloric acid on conhydrine:—$C_8H_{17}NO = C_8H_{15}N + H_2O$. It forms very vola-

tile, colourless needles, melts at 41° and boils at 168°. It is a secondary base of conine-like odour, and is a less active poison than the α-modification.

Poisoning by Conine and Hemlock.

Conine is an extremely powerful paralytic poison, which acts on the motor nerves; one drop is a distinctly poisonous dose, while ten drops may be fatal.

The symptoms produced by hemlock and conine are not uniform, and cases of poisoning are not numerous. Stupor, coma, and slight convulsions have been noticed, while in other cases the chief effect has been paralysis of the muscular system, especially of the legs. The pupils are somewhat dilated. After death the lungs are found filled with fluid blood and of a dark colour, and the stomach and intestines somewhat congested. The *post-mortem* appearances are not characteristic.

In toxicological inquiries the viscera and contents of the stomach should be treated as described under strychnine, the purified extract being agitated with soda and ether instead of ammonia and chloroform. From the ether, the alkaloid may be recovered by allowing the solvent to evaporate spontaneously in a cool place, or extracted as a salt by agitating the ether with dilute hydrochloric acid. From the purified salt of conine thus obtained, the free base may be again liberated by adding soda, and recognised by the mousy odour of hemlock developed immediately or on warming the liquid.

Conine may also be isolated from the viscera by the method used for the assay of hemlock. Otto in one case met with a volatile ptomaïne, which was very poisonous, but differed from conine in its reaction with platinic chloride. The seeds of *Lupinus luteus* (page 177) contain alkaloids somewhat resembling conine, but which do not yield the characteristic crystalline hydrochloride. Other of the *umbelliferæ* besides *conium* are possessed of poisonous properties, but it does not appear that conine has been proved to be the active principle.[1]

[1] *Œnanthe crocata*, or hemlock water-dropwort, is described by A. S. Taylor as one of the most virulent of English vegetable poisons. The leading symptoms produced are rapid insensibility, bloated and livid countenance, convulsive movements, stertorous breathing, dilated pupils, and *bloody foam about the mouth and nostrils.*

Cicuta virosa, water-hemlock or cowbane, produces symptoms similar to the above, including the foaming at the mouth. It is said to contain cicutine.

Sium latifolium and *S. angustifolium* have been mistaken for water-cress, with fatal results.

Æthusa Cynapium, the lesser hemlock or fool's parsley, appears

Assay of Hemlock and its Preparations.

Conine exists in all parts of the common or spotted hemlock, *Conium maculatum* (French, *la Ciguë;* German, *der Schieling*). It appears to be most abundant in the fruit, the proportion increasing with the maturity of the seeds. In hemlock *leaves*, R. Kordes found 0·24, and in the *fruit* 0·49 per cent. of alkaloid.

For the *extraction* of conine from hemlock, J. Schorm (*Ber.*, xiv. 1765) recommends that the seeds should first be swelled by hot water, and then moistened with a strong solution of sodium carbonate. The product is treated with steam, under a pressure of three atmospheres, as long as the distillate has an alkaline reaction, when it is neutralised with hydrochloric acid and evaporated to a weak syrup, which is shaken with twice its measure of strong alcohol and filtered from the precipitated ammonium chloride. The filtrate is distilled at 100°, a calculated amount of caustic soda ley added, and the mixture agitated with ether. (The residual aqueous liquid developes trimethylamine on prolonged standing, especially in summer.) The ethereal solution deposits large crystals of conhydrine when strongly cooled. This base is somewhat sparingly soluble in ether, and on distilling the solution passes over with the ether. The conine remaining in the retort is dehydrated with potassium carbonate, and purified by fractional distillation. The first 10 per cent. boils between 110° and 168° C., and is very impure. The next 60 per cent., boiling between 168° and 169°, is pure conine; while the next 20 per cent., boiling between 169° and 180°, is impure. The thick dark liquid left in retort contains conhydrine.

A purer product, but somewhat lower yield, is said to be obtained by exhausting the hemlock seeds with acetic acid, and evaporating the solution to a syrup in a vacuum. Magnesia is then added, and the mixture agitated with ether, which extracts the alkaloid.

Many specimens of conium leaves and seed are almost inert from the loss of their volatile active constituent, and hence a method of assay is of considerable importance, and ought to have a place in the *Pharmacopœia.*

For the *determination* of the conine and associated alkaloids in hemlock, R. A. Cripps (*Pharm. Jour.*, [3], xviii. 13, 511) recommends the following process:—A weight of 5 grammes of the finely-powdered fruit is mixed with an equal weight of sand, and extracted with a mixture of 25 c.c. of nearly absolute alcohol,

to contain an energetic poison, though this has been disputed by Harley (*St Thomas's Hospital Reports*, new series, iv. 68; x. 257), and also by Tanret, who believes the erroneous statements respecting it to have arisen from a confusion of the plant with *Conium maculatum*, which it closely resembles.

15 c.c. of chloroform, and 10 c.c. of a saturated solution of dry hydrochloric acid gas in chloroform. The liquid is separated from the marc[1] and agitated with two separate quantities of 25 c.c. of distilled water. The aqueous liquid now contains the conine as hydrochloride. It is shaken once with chloroform, then rendered alkaline with caustic soda, and extracted three times by agitation with chloroform. The chloroform is washed by agitation with alkaline water, and is then run into a solution of hydrochloric acid gas in ether. This is evaporated in a current of air, and the residue dried at a temperature not exceeding 90° C. The conine hydrochloride obtained should be crystalline, and almost perfectly white. From its weight the proportion of conine can be calculated, 163·5 of the hydrochloride representing 128·0 of the base. If, after weighing the residue, the hydrochloric acid be determined by titration with silver nitrate, using potassium chromate as an indicator, the difference will be the weight of alkaloid, and the result should closely correspond with that previously calculated.

The foregoing process may be shortened by agitating the washed chloroformic solution of the conine as liberated by caustic soda with water, and gradually adding decinormal hydrochloric acid until a slight acid reaction to methyl-orange is developed, which does not disappear on again shaking. Each c.c. of decinormal acid used represents 0·0128 gramme of alkaloid, in terms of conine. Petroleum spirit may be substituted for the chloroform.

For the estimation of the alkaloids in *Tincture of Conium*, Farr and Wright (*Pharm. Jour.*, [3], xxi. 857) evaporate 50 c.c. of the preparation to a low bulk at 100° C. with 1 c.c. of normal sulphuric acid. The residual liquid is diluted somewhat, and twice shaken with chloroform. It is then rendered alkaline with ammonia, and the liberated alkaloids shaken out with chloroform. The chloroformic solution is freed from traces of ammonia by agitation with water, separated and run into a solution of dry hydrochloric acid gas in chloroform, taking care that the orifice of the separator dips below the surface of the acid chloroform, which is then evaporated, and the residue dried at 90° and weighed, as recommended by Cripps. The proportion of *total alkaloid* contained in the tincture of conine, as assayed by this process, is from 0·07 to 0·10 per cent. The proportion in the extract ranges from ½ to nearly 3 per cent.

[1] The exhaustion should be proved to be complete, by treating the marc with water, and testing the solution with iodine and with Mayer's solution, neither of which should produce more than the faintest turbidity; and the dried marc should give a barely perceptible odour of conine when warmed with caustic soda.

Lupine Alkaloids.

From the different species of l u p i n e several alkaloids have been isolated, some of which, at any rate, belong to the class of volatile alkaloids, and in their odour and other characters appear to be related to conine.

Lupinine, $C_{21}H_{40}N_2O_2$, or $C_{21}H_{38}N_2(OH)_2$. As isolated by G. Baumert from the seeds of *Lupinus luteus*, lupinine is a readily crystallisable base, melting at 67°·5–68°·5, and boiling with some decomposition at 255°–261°. In a stream of hydrogen it distils unchanged at 255°–257°, and is also volatile with steam. Lupinine has a pleasant apple-like odour and an extremely bitter taste, the latter character extending to its salts. It has a paralysing effect on the nerve-centres. Lupinine is lævo-rotatory, easily soluble in cold water and alcohol, but less soluble in warm water. From its aqueous solution it is separated by excess of caustic alkali. Lupinine dissolves readily in ether, chloroform, and benzene. Carbon disulphide dissolves the base while acting chemically upon it.

Lupinine is highly caustic, and is a strong base, liberating ammonia from its salts and fuming with hydrochloric acid. $B(HCl)_2$ forms large rhombic crystals. BH_2PtCl_6 is crystalline and soluble in water. The *aurochloride*, $B(HAuCl_4)_2$, forms needles, difficultly soluble in water, but readily in alcohol. The *nitrate*, $B(HNO_3)_2$, forms rhombic crystals, very soluble in water and alcohol.

Metallic sodium dissolves in melted lupinine with evolution of hydrogen, forming a s o d i u m - d e r i v a t i v e, decomposed by water into lupinine and sodium hydroxide. When heated with acetic anhydride, lupinine yields $C_{21}H_{38}N_2(C_2H_3O)_2$, as an oil, insoluble in water and very easily saponified.

When lupinine is heated to 150°–180° for ten or twelve hours with fuming hydrochloric acid, or the hydrochloride to 175° with phosphoric anhydride, it yields *anhydrolupinine*, $C_{21}H_{38}N_2O$, as a highly oxidisable fluid base, smelling like conine. BH_2PtCl_6 forms red quadratic tables, easily soluble in water and dilute alcohol. *Dianhydrolupinine*, $C_{21}H_{36}N_2$, results when lupinine is heated with fuming hydrochloric acid to 200° C. It is a highly oxidisable oil, boiling at 220°, and forming a c h l o r o p l a t i n a t e, crystallising in dark red needles. *Oxylupinine*, $C_{21}H_{40}N_2O_5$, is formed, together with anhydrolupinine, by the action of phosphoric anhydride on lupinine hydrochloride. It is a yellowish, disagreeable smelling oil, boiling with some decomposition at 215°.

Arginine, $C_6H_{14}N_4O_2$, is contained in the seeds of *L. luteus* which have germinated in the dark. It forms crystalline salts, evolves nitrogen with nitrous acid, and yields urea when boiled with baryta-water.

LUPINIDINE, $C_8H_{15}N$, is a base found by Baumert in the yellow lupine. It forms a volatile, oxidisable, viscous oil, having an odour of hemlock. It is intensely bitter and feebly poisonous, producing symptoms like those of *curare*. Lupinidine forms a crystalline hydrate, B,H_2O, very insoluble in water. The salts are crystallisable. No acetyl-derivative is obtainable.

LUPANINE, $C_{15}H_{25}N_2O$, is an alkaloid obtained by M. Hagen (*Liebig's Annalen*, ccxxx. 367; *Jour. Chem. Soc.*, l. 163) from the seeds of the blue lupine, *Lupinus angustifolius*, which are stated not to contain lupinine or lupinidine. It is described as a pale yellow, honey-like syrup, with green fluorescence, intensely bitter taste, and an unpleasant odour like that of hemlock. Lupanine does not boil at 290°, even under the reduced pressure of 130 mm. It has a strong alkaline reaction, attacks the skin, expels ammonia from its salts, and forms with hydrochloric acid white fumes of the hydrochloride. With excess of cold water, lupanine forms a turbid solution, from which the base is almost entirely separated on heating. It dissolves with difficulty in cold alcohol, but readily in ether, chloroform, and petroleum spirit. *Lupanine hydrochloride*, $BHCl + 2aq.$, forms hygroscopic, quadratic crystals, melting at 127°, and soluble in alcohol but not in ether. BH_2PtCl_6 is not distinctly crystalline. $BHAuCl_4$ forms golden needles, insoluble in water, alcohol, or ether. From solutions of its salts, lupanine is precipitated by caustic potash and soda, but not by ammonia.

From the seeds of *Lupinus albus*, Campani isolated a poisonous liquid alkaloid, boiling at 210°–218°. From the same source Betelli obtained a crystallisable base.

According to O. Kellner (*Bied. Centr.*, x. 97) lupine seeds can be deprived of the whole of their bitter constituents, and rendered much more palatable and wholesome, by soaking them in water for twenty-four hours, steaming them for one hour, and then washing them for two days. Kühn has shown that the substances which cause lupine sickness are destroyed by steaming.

Nicotine. Nicotia. $C_{10}H_{14}N_2$; or $C_5H_7N.C_5H_7N$.

Nicotine has the constitution of a hexahydro-dipyridyl (see page 164). It is the poisonous basic principle of tobacco, in which it exists combined with malic and citric acids (compare page 184), in proportions varying within very wide limits.

Pure nicotine is a colourless, oily fluid of 1·011 specific gravity at 15° C. On prolonged exposure to air it becomes yellow, and eventually resinoid. It has a sharp caustic taste, is intensely poisonous, and has a strong and unpleasant odour, recalling that of tobacco. Nicotine boils at about 250° C., with partial decom-

position, but it distils readily with the vapour of water or alcohol, and volatilises to a notable extent at the ordinary temperature. Nicotine absorbs moisture from the air, and evolves heat when mixed with water, diminution in volume simultaneously occurring.[1]

Skalweit (*Ber.*, xiv. 1809) has given the following figures showing the specific gravity of mixtures of nicotine and water. His results point to the existence of a hydrate of nicotine.

Nicotine.	*Water.*	*Specific Gravity at 15° C.*
100	0	1·011
100	5	1·017
100	10	1·024
100	20	1·030
100	30	1·034
100	40	1·037
100	50	1·040
100	60	1·038
100	70	1·033

Nicotine has a powerful lævo-rotatory action on polarised light, the value of S_D in 20 per cent. aqueous solution being, according to Pribram, $-161°\cdot55$. The rotation diminishes rapidly but irregularly by further dilution. Thus for a 4 per cent. solution the value S_D is $-77°\cdot03$, while below this strength an increase is observed, S_D being $-79°\cdot32$ for a solution of 0·8826 specific gravity. The rotation is affected by time, not reaching its maximum for 48 hours (*Ber.*, xx. 1840).

The aqueous solution of nicotine is powerfully alkaline in reaction. The nicotine is partially separated by addition of excess of caustic potash or soda (compare pyridine). Nicotine in aqueous solution, and in the absence of other free base, can be determined by titration with standard acid and methyl-orange.

Nicotine forms two classes of salts. The monacid salts are stable and neutral to litmus and methyl-orange, but the diacid salts have an acid reaction. Most of the salts of nicotine crystallise with difficulty. The *acid tartrate*, $C_{10}H_{14}N_2(C_4H_6O_6)_2 + 2aq.$, is an exception, and forms handsome tufts when ether is added to its alcoholic solution.

DETECTION AND DETERMINATION OF NICOTINE.

Alcohol dissolves nicotine in all proportions, and on evaporating

[1] When water is added to solution of nicotine containing less than 20 per cent. of base, the mixture becomes turbid and clears only on long standing. On heating to 40° the liquid clears rapidly, but becomes again turbid when cooled or further heated to 50°. Between 50° and 60° the turbidity amounts to milkiness, which disappears when the liquid is cooled below 50°. At 70° the nicotine separates in part as an oily layer.

or distilling the solution the alkaloid is found chiefly in the first fractions. It is extracted from its aqueous alkaline solutions by agitation with ether, chloroform, benzene, amylic alcohol, or petroleum spirit, and may be recovered from the solvent by separating and agitating with dilute acids. If oxalic acid be employed, the resultant solution may be evaporated to dryness and treated with alcohol, which dissolves the nicotine oxalate while leaving any ammonium oxalate undissolved. After again removing the alcohol by evaporation, the nicotine may be liberated from the warm liquid by adding excess of caustic soda, when the characteristic tobacco-like smell of nicotine will be observed, and the alkaloid can be obtained pure by distilling the liquid with water, or agitating it with ether and allowing the separated solvent to evaporate spontaneously in a cool place.

Treated with nitric acid, nicotine yields a thick reddish liquid. Sulphuric acid produces no change in the cold, but a brown colour is developed on heating.

On dissolving nicotine in dilute hydrochloric acid, and adding platinic chloride, *nicotine chloroplatinate*, $C_{10}H_{14}N_2,H_2PtCl_6$, is thrown down as a sparingly soluble, yellowish, crystalline compound. The precipitate is soluble in hot water, especially in presence of free hydrochloric acid. Addition of alcohol increases the delicacy of the test, and the formation of the precipitate is much facilitated by stirring the liquid. A m m o n i a gives a similar reaction, but c o n i n e yields no precipitate with platinic chloride.

Picric acid, if added *in excess* to solution of nicotine, throws down *nicotine picrate* as an amorphous yellow precipitate, which rapidly changes to a mass of crystalline tufts, even in presence of foreign organic matter.

Nicotine is precipitated by Mayer's reagent (page 138) from very dilute solutions; and, by operating in strongly acid liquids, Z i n o f f s k y obtained very good quantitative results. The formula of the precipitate is $C_{10}H_{16}N_2HgI_4$, and 1 c.c. of the reagent represents 0·00202 gramme of nicotine.

On adding mercuric chloride to a solution of nicotine a white *crystalline* precipitate is produced, soluble in dilute hydrochloric or acetic acid. This is the most characteristic reaction of nicotine. S t r y c h n i n e produces a similar precipitate, nearly insoluble in acetic acid. Many other alkaloids are precipitated, but the compounds are almost invariably amorphous. This is the case with the precipitate produced by conine, which is almost the only alkaloid which will distil over with nicotine on boiling the solution with a slight excess of caustic soda. A m m o n i a, however, behaves like nicotine, and must, if necessary, be separated before applying the

test. Ammonia is sharply distinguished from nicotine, conine, and lobeline by adding a solution of iodine in iodide of potassium to the slightly *acidulated* solution of the base. Ammonia produces no change, but with either of the vegetable alkaloids a brown or brownish red precipitate will result. Iodine solution will detect 1 of nicotine in 250,000, and is the most delicate reagent known for the alkaloid.

Solutions of nicotine are not precipitated by chromates, ferrocyanides, ferricyanides or thiocyanates, nor by gallic acid. With gallotannic acid an aqueous solution of nicotine yields a white, amorphous precipitate, which readily dissolves on cautious addition of hydrochloric acid, but is again precipitated by further addition of acid, and is then insoluble even in a large excess. Tannate of nicotine is readily soluble also in acetic and nitric acids, but is not reprecipitated on adding an excess.

A variety of processes have been devised for the determination of nicotine in *tobacco* and its preparations. The problem is complicated by the presence of ammonium salts, by the difficulty of completely extracting nicotine from aqueous liquids by agitation with immiscible solvents, and by the tendency to form an emulsion when these are used, owing to the presence of pectinous matter. The methods proposed have been reviewed by J. Biel (*Pharm. Zeit. Russ.*, xxvii. 3; *Analyst,* xiii. 97), who recommends the following process, which is a modification of that proposed by Kissling:—100 grammes of powdered tobacco-leaves, or 10 to 20 grammes of extract of tobacco, are mixed with slaked lime and distilled in a current of steam until the condensed steam is no longer alkaline. The distillate, which will measure about ½ litre, is rendered faintly acid with dilute sulphuric acid, evaporated to 50 c.c., made alkaline with caustic soda, and agitated six times with ether, using 20 c.c. each time. Biel then distils off the greater part of ether slowly, adds excess of decinormal sulphuric acid, and titrates back with decinormal soda, using rosolic acid as an indicator. The object in distilling off the ether is to get rid of any traces of ammonia which may be present; but it is difficult to do this without risking the volatilisation of some of the nicotine. It is preferable to titrate the unconcentrated ethereal solution by gradually adding decinormal sulphuric acid, using methyl-orange as an indicator, and agitating between each addition. Each c.c. of decinormal acid neutralised represents 0·0162 gramme of nicotine. The results will be high if ammonia be present, and in such case the neutralised aqueous liquid should be separated from the ether, and evaporated to dryness at 100°. The residue is weighed and treated with absolute alcohol, which will dissolve the sulphate of nicotine, while any ammonium sulphate will be

left insoluble, and its weight can be deducted from the weight of the mixed sulphates previously found, the difference being the sulphate of nicotine. The result may be confirmed by adding phenolphthaleïn to the alcoholic solution of nicotine sulphate and titrating with decinormal alkali, which will react just as if the sulphuric acid were uncombined.

From conine, nicotine is distinguished by its odour, by being heavier instead of lighter than water, and by the reactions with hydrochloric acid gas, mercuric chloride, argentic nitrate, platinic chloride, and picric acid (see above, and page 181).

POISONING BY NICOTINE AND TOBACCO.

Nicotine is one of the most violent poisons known. Only a few instances are on record of poisoning of the human subject by the pure alkaloid, but the effects of *tobacco*, which owes its poisonous properties entirely to nicotine, are well known.[1] Impure solutions of nicotine and infusions of tobacco are employed as insecticides.

"The usual effects of a poisonous dose of tobacco, when taken into the stomach, are confusion in the head, paleness of the countenance, vertigo, nausea, severe retching and vomiting, heat in the stomach, great anxiety, a sense of sinking at the pit of the stomach with extreme prostration, trembling of the limbs, and sometimes violent purging. The pulse is small, feeble, and almost imperceptible; the respiration difficult, and the skin cold and clammy; the pupils are generally dilated, but sometimes contracted, and the vision is usually more or less impaired. Death is often preceded by convulsions and paralysis" (T. G. Wormley, *Micro-chemistry of Poisons*).

In toxicological investigations, nicotine may be isolated from the viscera in the same manner as conine (pages 170, 175). An alternative method is to digest the suspected matters with water acidulated with acetic acid, and treat the filtered liquid with excess of lead acetate. The liquid is again filtered, the lead removed from the filtrate by passing sulphuretted hydrogen, and the clear solution treated with caustic soda, separated from any precipitate, and distilled, when a fluid having the odour and exhibiting the reactions of nicotine will be obtained. Any supposed nicotine which may be isolated should be tested by placing it on the tongue of a young rabbit or small bird, when tremors, paralysis, and

[1] When tobacco is smoked, the greater part of the nicotine is converted into pyridine and other pyrogenous compounds, and the entire decomposition of the nicotine is sometimes asserted; but Melsens appears to have fully proved the presence of unchanged nicotine in tobacco smoke in a proportion equal to about one-seventh of that present in the original tobacco (compare page 193).

convulsions will rapidly ensue. Nicofine appears to be unchanged by putrefaction, and hence may be detected in the tissues long after death.

TOBACCO (French, *le Tabac;* German, *der Tabak*).

Tobacco is the dried leaf of *Nicotianum Tabacum* and allied species.[1]

According to S. W. Johnson, a good crop of tobacco, yielding 1260 lbs. of dry leaf and 1110 lbs. of dry stalk, removes from the soil the following constituents in lbs. per acre:—

Constituents.	*Leaves.*	*Stalks.*	*Total.*
SO_3,	14	3	17
P_2O_5,	7½	15	22½
CaO,	73	15	88
MgO,	17	2	19
K_2O,	71	47	118
Na_2O,	5	10	15
Sum of Ash Constituents,	206	95½	301½
Nitrogen,	49	33	82

As the stalks are returned to the land, tobacco is not a very exhausting crop, but requires abundant manuring, since the period of growth does not exceed three months. Hence, rye may be advantageously sown as soon as the tobacco is off, and ploughed in as a green crop when cultivation for tobacco commences.

Besides cellulose, albuminoid compounds, pectic acid, gum-resins, and other ordinary plant-constituents, the leaf of tobacco contains a peculiar volatile, crystalline principle called nicotianin or tobacco-camphor, to which the formula $C_{23}H_{32}N_2O_3$ has been attributed. Tobacco also contains the volatile alkaloid nicotine, which is apparently peculiar to the genus. This base exists in combination with malic acid, but the presence of citrates, acetates, and oxalates has also been established.[2] Fresh tobacco-leaves (especially the midribs) contain a notable proportion of nitrates, but these salts are said to disappear during the process of fermentation to which manufactured tobacco is subjected. This fermentation has for its object the destruction or modification of some of the natural

[1] The genus *Nicotiana* contains more than 70 species. *N. Tabacum* yields the tobacco of Havana, Cuba, France, Holland, Belgium, &c. *N. rustica* furnishes East Indian tobacco, and the kinds known as Latakia and Turkish tobacco. Tumbeki or Persian tobacco is the product of *N. Persica.*

[2] From 100 grammes of dried tobacco-leaves, Goupel obtained from 3 to 4 grammes of acid malate of ammonium. J. Takayama (*Chem. News,* l

constituents, and the formation of "ferment oils," which probably contribute to the aroma, especially when saccharine matter,

300) obtained the following percentage results by the analysis of Japanese tobacco :—

	Nagato.	Shimozuki.	Settzu.	Osumi.
Water, ...	8·41	10·01	7·68	18·18
Ash, ...	15·76	8·45	20·71	9·80
Nicotine, ...	2·45	8·02	3·92	1·89
Acetic acid, ...	0·05	0·04	0·01	0·08
Oxalic acid, ...	trace	0·27	0·25	trace
Malic acid, ...	0·79	1·02	1·83	2·98
Citric acid, ...	0·52	0·59	0·92	0·89
Pectic acid, ...	1·24	5·84	7·42	2·35

In the above analyses, the *nicotine* was extracted by ammoniacal ether, the solvent distilled off, and the nicotine in the residue determined by titration. For the *acetic acid*, the powdered tobacco was moistened with water and tartaric acid, and distilled in a current of steam, the acetic acid being determined in the distillate. For the fixed organic acids, 10 grammes of the sample was moistened with sulphuric acid in the quantity requisite to combine with the bases (as indicated by the carbonates in the ash), and exhausted with ether. From the ethereal solution the acids were extracted by a small quantity of water, the separated aqueous liquid rendered alkaline with ammonia, acidulated with acetic acid, and the oxalic acid precipitated by adding calcium acetate. To the filtrate, a dilute solution of lead acetate was gradually added, until a test quantity of 1 c.c. of the supernatant liquid gave, on further addition of lead acetate, a precipitate which was completely soluble in a few drops of acetic acid. The liquid was then filtered, and the precipitate of lead citrate washed with water containing a little lead acetate and acetic acid, and then with alcohol, the washings being kept separate. The *citric acid* was deduced from the weight of lead oxide left on igniting the precipitate. From the filtrate, the *malic acid* was precipitated by excess of lead acetate solution, and its amount deduced from the weight of lead oxide left on ignition. The washings from the precipitate of lead citrate were boiled to expel alcohol and treated with excess of lead acetate, the precipitate being regarded as a mixture of lead *citrate* and *malate* in equal proportions (compare Vol. I. page 434).

The *pectic acid* was determined by exhausting 10 grammes of tobacco with rectified spirit containing one-fourth of its volume of concentrated hydrochloric acid. The residue was washed with spirit till the hydrochloric acid was wholly removed, and then treated with a solution of a known weight of ammonium oxalate, by which the pectic acid was dissolved. After digesting for two hours at 35°, the liquid was filtered, the residue washed, and the filtrate diluted to 1 litre. An aliquot part of this was precipitated by calcium acetate, and the precipitate washed and dried at 100°. The weight of lime left on igniting the precipitate was then ascertained. The weight of CaO and the oxalate in the precipitate being known, the *pectic acid* corresponded to the difference.

liquorice or alcohol is added during the maceration to which the tobacco is subjected.[1]

As sold by the farmers, the tobacco-leaves contain about 30 per cent. of water. When the fresh leaf is simply dried, the product is yellow, the brown colour of commercial tobacco being due to the regulated fermentation already alluded to. The unmanufactured tobacco imported into England is converted into roll or spun tobacco, cut tobacco, and cigars, the refuse being used for making snuff. In the manufacture of roll-tobacco, the leaves are moistened with water, spun into various sizes of twist, made up into rolls, and pressed. The liquid or juice which exudes is used as a sheep-dip. Cut tobacco is made by moistening the leaves, cutting them to the required size, and drying on plates; or it may be made into cakes first, and afterwards cut. The Excise regulations prohibit the use of any foreign matter in manufacturing tobacco, besides water and a little oil. Hence, except in the proportion of water, which is not allowed to exceed 35 per cent. (as estimated by drying at 100° C.), there is no tangible difference between manufactured tobacco and the dried leaves imported. The proportion of nicotine in tobacco does not appear to be an index of the quality.

J. Clark (*Jour. Soc. Chem. Ind.*, iii. 554) has published the percentages of *ash* yielded by the ignition of twenty-one authentic

	In 100 Parts of the Dry Substance.		
	Total Ash.	Soluble Ash, "Alkaline Salts."	Sand.
WHOLE LEAF :—			
Highest,	30·80 *	11·37	12·32 *
Lowest,	13·79	2·40 †	0·13
Average,	20·32	6·47	2·48
LAMINÆ :—			
Highest,	31·07 *	8·09	14·41 *
Lowest,	12·47	1·66 †	0·09
Average,	19·21	4·98	2·86
MIDRIB :—			
Highest,	30·37 *	20·01	4·91 *
Lowest,	15·44	4·63	0·12
Average,	21·92	11·41	1·15

* Paraguay Tobacco. † Chinese Tobacco.

samples of representative tobacco-leaves. The table is an abstract of his figures, which in all cases refer to the leaf dried at 100° C.

[1] Schizomycetes occur in fermented tobacco in large numbers, but the number of species is very limited. Trial experiments by E. Suchsland, with foreign ferments on German tobacco-leaves, yielded a tobacco not recognisable as of German origin.

As the composition of the laminæ and of the stem or midrib of the leaf differ materially, these were carefully separated before analysis.

E. Quajat (*Bied. Centr.*, 1880, p. 345) found the ash of fourteen samples of dry tobacco (including both superior and common kinds) to range from 31·03 per cent. in a Bassano sample to 17·11 in Virginian and 16·78 per cent. in Turkish. He considers that the quality of tobacco varies inversely with the ash, but Nessler recognises no relation between the two.

Irby and Cabell (*Chem. News*, xxx. 117) have published the figures obtained by the analysis of six typical samples of Virginian tobacco. All were in the leaf state, free from stalk, but retaining the midrib. No. 1 was light yellow tobacco, "coal-cured wrappers" for cigars; No. 2, light yellow, "fine smoking" tobacco; No. 3 was medium brown colour, "sweet fillers" for cigars; No. 4 was dark, "Austrian and Italian cigar wrappers;" No. 5, dark "English shipping;" and No. 6, dark, "exported to France for snuff." These samples when air-dried yielded:—

	No. 1.	No. 2.	No. 3.	No. 4.	No. 5.	No. 6.
MOISTURE, per cent., . . .	7·91	1·00	11·67	9·93	13·74	9·71
ASH, total, per cent. *on tobacco*, .	11·80	15·39	18·52	16·31	18·18	15·90
,, Soluble in HCl, per 100 of ash,	70·71	63·17	60·93	84·40	64·53	66·66
,, Sand and charcoal, ,, ,,	5·30	14·69	16·98	7·92	8·82	8·97
,, Carbon dioxide, ,, ,,	23·99	22·14	22·09	7·68	26·65	24·37

Deducting the sand, carbon, and carbon dioxide, as also the small proportions of alumina and ferric oxide found in the portion of the ash soluble in acid, the "pure ash" of the tobacco was calculated. The total nitrogen was determined by the absolute method of Dumas, and the nicotine by Mayer's solution, with the following results, expressed on 100 parts of tobacco dried at 100° C.:—

	No. 1.	No. 2.	No. 3.	No. 4.	No. 5.	No. 6.	Average.
Pure ash, ...	8·94	9·29	12·34	14·84	13·39	11·06	11·64
Total nitrogen, . . .	3·18	2·63	3·72	5·76	5·33	5·26	4·32
Nicotine, ...	3·32	3·59	5·28	7·09	6·20	8·86	5·72
Nitrogen in forms other than nicotine, .	2·61	2·01	2·81	4·54	4·26	3·73	3·33
Percentage of total nitrogen present as nicotine,	18·2	23·6	24·5	21·3	20·1	28·9	22·8

The following table shows the average proportions of nitrogen

and ash, and the composition of the latter in tobacco from various sources :—

	VIRGINIA.	KENTUCKY.	NEW ENGLAND.	EUROPEAN (including Turkish).
Observer,	Irby & Cabell.	Peter.	S. W. Johnson.	E. Wolff.
Number of specimens contributing to average,	6	30	12	13
Nitrogen, per cent.,	4·32	...	4·24	...
"*Pure ash*," per cent.,	11·64	12·83	16·56	...
Percentage composition of ash—				
SiO_2,	1·72	2·73	0·84	10·29
Cl,	2·81	3·74	9·36	4·92
SO_3,	5·49	4·21	6·58	4·30
P_2O_5,	3·30	4·99	3·56	3·21
K_2O,	35·58	37·57	34·96	18·01
Na_2O,	2·78	2·10	1·99	4·29
CaO,	37·60	35·31	34·48	43·51
MgO,	10·72	9·85	8·21	11·46

Will and Fresenius (*Ann. Chem. Pharm.*, l. 387) have recorded the results of their analyses of the ash of a number of samples of Hungarian tobacco, and Schloesing (*Jour. Pract. Chem.*, lxxxi. 148) the proportions of potash, lime, magnesia, sulphates, and chlorides in the ash of tobacco grown on different soils. The proportion and composition of the ash of English tobacco has been investigated by A. Wingham (*Jour. Soc. Chem. Ind.*, vi. 76, 400), of Indian and Burmese tobaccos by R. Romanis (*Chem. News*, xlvi. 248), and of various kinds of tobacco grown in Japan by J. Takayama (*Chem. News*, l. 301), and Fesca and Imai (*Jour. Soc. Chem. Ind.*, vii. 759).

The combustibility of tobacco is profoundly affected by the proportion and nature of the universal constituents, especially the calcium and potassium, and the forms of combination in which these metals occur. The ash of the more combustible tobaccos is comparatively rich in potassium carbonate, showing the presence of a large proportion of organic salts of potassium in the original tobacco, while the ash of tobacco of inferior burning quality contains a larger proportion of sulphates or chlorides, and hence proportionately less alkaline carbonates. According to Schloesing and Nessler tobacco burns best when it contains a considerable proportion of potassium malate, which is a natural constituent of the leaf; but the effect may be imitated, and a slow burning tobacco improved, by the addition of potassium acetate or other organic salt of potassium, while the combustibility may be diminished by addition of sulphate of calcium or magnesium. According to E. R. Durrwell the whiteness of the ash of good tobacco is

due to the presence of a large proportion of alkaline salts, which swell up as the tobacco burns, and tear the fibres, thereby inducing complete combustion. Sulphates rather favour proper combination, while nitrates are prejudicial. Chlorides are regarded by most observers as objectionable, and hence should be absent from fertilisers intended for application to tobacco crops.[1]

A. Mayer (*Land. Versuchs-Stat.*, xxxviii. 127; *Jour. Chem. Soc.*, lviii. 1458) has investigated the influence of various substances employed in 0·5 per cent. solution on the combustibility of ordinary filter-paper. Organic substances of the most different kinds were found favourable to combustion with flame and to diminish the power of glowing, while inorganic substances usually had the opposite effect.[2]

From his experiments with filter-paper, Mayer concludes that the more ash tobacco yields, and especially the more potassium carbonate (representing organic salts of potassium in the tobacco), the better the tobacco will burn; while much calcium phosphate, sulphate, or chloride is held to be prejudicial. The alkalinity of the ash is a better measure of combustibility than the proportion of chlorine. Mayer gives the following figures obtained by the partial analysis of tobacco of different qualities from Sumatra.

TOBACCO.	CHLORINE.	Total POTASH.	ALKALINITY as K_2CO_3.	ASH.	NITROGEN.
Good,	1·5	5·9	4·9	20·5	2·7
Sufficiently good (light ash),	0·5	5·8	6·8	20·8	3·2
Sufficiently good,	0·7	6·6	5·5	22·5	2·0
Sufficiently good (grey ash),	1·2	7·9	4·1	17·7	3·3
Bad,	3·3	4·6	0·5	18·5	2·6

[1] G. Cantoni (*Bied. Centr.*, 1879, p. 812) found that nitrates of the alkali-metals had most effect as regarded vigour of growth of the tobacco, while alkaline chlorides and gypsum were prejudicial, the yield in weight being actually higher when no manure was applied than when ammonium sulphate or sodium chloride was added. The leaf was almost totally incombustible when the plant had been manured with gypsum, but that produced by manuring with potassium sulphate was completely combustible. A. Mayer confirms the statement that chlorides are objectionable in tobacco manures, and states that their use increases the proportion of chlorine in the leaves from 0·21 to 0·52 per cent.

[2] The salts found most favourable for glowing were the alkaline nitrates, sulphates, and carbonates; alkaline organic salts; and potassium chloride. Sodium salts had less effect than potassium salts, and calcium and magnesium salts much less still. Paper treated with potassium salts, magnesium sulphate, or sodium carbonate gave a white ash. Chlorides were found rather to favour glowing.

According to J. M. van Bemmelin (*Land. Versuchs-Stat.*, xxxvii. 409; *Jour. Chem. Soc.*, lviii. 1338), tobacco which burns badly either contains an excess of chlorine and sulphuric acid over the potash, or else the amount of potassium, compared with that of chlorine and sulphuric acid, is low, owing to the potash being partially replaced by soda. Leaves of the best quality contain little or no soda, not much chlorine or sulphuric acid, but a large proportion of organic salts of potassium, calcium, and magnesium. Too much fat or albumin in the tobacco neutralises the good effect of organic salts of potassium, and it is important that the albuminoids and carbohydrates should be sufficiently decomposed during the casing of the tobacco. In the ash the ratio of $CO_2 : Cl + SO_3$ is not less than 7 : 1, and the ratio of $K : Cl + SO_3$ is not less than 2 : 1.

According to Mayer, tobacco which burns badly can be made to burn well by steeping it for twenty-four hours in a 0·5 per cent. of potassium acetate or nitrate. In this way soluble organic matter and alkaline chlorides are extracted, while the salts favourable to glowing are taken up. By steeping in a 0·5 per cent. solution of calcium acetate, the most incombustible tobacco, which can otherwise only be used for snuff, can be made to burn well, and yield a perfectly white ash.

The mode of existence of the *nitrogen* in tobacco has been investigated by Fesca and Imai (*Jour. Soc. Chem. Ind.*, vii. 759), who have published the following among other interesting analytical data :[1]—

	Highest Percentage.	*Lowest Percentage.*	*Average of 8 Samples.*
In air-dried tobacco—			
Sand,	1·91	1·02	1·48
Moisture,	12·21	8·39	10·46
In dry, sand-free tobacco—			
Pure ash,	14·64	10·68	12·82
Containing soluble CO_2,	0·57	0·84	0·44
" insoluble CO_2,	4·19	8·05	3·54
" K_2O,	4·73	8·14	3·97
Crude fat,	14·44	10·34	12·12
Crude fibre,	15·50	13·17	14·10
Total nitrogen,	1·69	1·29	1·44
Amido-nitrogen,	0·67	0·32	0·48
Albuminoids,	3·62	0·69	2·58
Nicotine,	4·09	2·63	3·16
Per 100 *parts of total nitrogen*—			
N as amido-compounds,	41·3	23·2	32·7
N as albuminoids,	40·0	9·6	29·2
N as nicotine,	48·6	29·7	38·1

[1] Fesca and Imai deduce the following conclusions from their researches :—The quantity of nicotine may be considered as bearing the same relation to tobacco as the percentage of alcohol does to spirituous liquors; but as yet a

The aqueous infusion of tobacco contains a body which reduces Fehling's solution. According to T. J. Savery (*Chem. News*, xlix. 123), the reducing body is almost entirely precipitated by basic lead acetate, the filtrate being without action on Fehling's solution. The body precipitated by lead acetate is probably caffetannic acid, and amounts, according to J. Attfield (*Pharm. Jour.*, [3], xiv. 541), to about 3 per cent. of the tobacco. But Attfield states that the solution after treatment with basic

high percentage of nicotine has not been shown to be an indication of the good quality of tobacco. Nitric acid should not be found in well-fermented tobaccos. Ammonia determinations are frequently too high, as they include some amido-nitrogen. 0·1 per cent. or so of ammonia does not seem to lower the quality of the tobacco. The albuminoids in a tobacco afford no indication of quality unless the proportion of amides is simultaneously considered. The amido-nitrogen represents for the most part harmless, or, perhaps, even beneficial, nitrogenous compounds. It is possible that a further study of these bodies and their decompositions will reveal the presence of bodies exercising a direct influence on the quality of tobacco. Anyway, the conversion of albuminoids into amides is one of the most important results of the fermentation. Ordinary fat determinations, or rather extracts, are of no use in tobacco analysis. Carbohydrates should not be present in well-fermented tobacco, but a study of the changes they undergo would doubtless be of great value in connection with tobacco. Only considerable differences in the amount of the various constituents of tobacco can give any conclusive indication of the quality of a tobacco. Very bad tobaccos always contain much albuminoid matter, sulphuric acid, chlorine, and large quantities of mineral acids, with small proportions of amido-nitrogen, potash, &c. By the present methods of analysis it is easier to recognise a bad tobacco than one of good quality. Bases, particularly potash and lime, in medium quantity, are favourable to the good quality, and especially the combustibility, of tobacco. An excess of either of these bases over a liberal mean percentage is neither a sign of good quality nor combustibility, and only an exceptionally low percentage of either of them can be regarded with certainty as a bad sign. Very high magnesia is prejudicial to the combustibility. Mineral acids in large quantities indicate both bad combustibility and quality; but only a very high proportion of an individual acid can be safely considered a decidedly bad indication. The combustibility is influenced to the greatest extent by the quantity of sulphuric acid present, and in a diminishing degree by the percentage of chlorine, phosphoric acid, and silica in the tobacco. The percentage of soluble carbonates appears to have no important influence on the quality and combustibility of tobacco; the influence of the total quantity of carbonates in the ash is much greater, but even in this there is a maximum beyond which the percentage of carbonic anhydride in the ash cannot be regarded as indicating increase of combustibility. The relation of carbonates to the mineral acids is a much more important factor, a large preponderance of the former being a favourable sign. High basicity of ash is an excellent indication of good combustibility, especially when not due either entirely, or to a great extent, to magnesia or iron.

lead acetate still contains a sugar-like body, which he did not attempt to isolate, and which had little or no optical activity, but which yielded alcohol on fermentation with yeast, in amount corresponding to an average of 7 per cent. of sugar. Eastes and Ince (*Pharm. Jour.*, [3], xvi. 682) found a small percentage (2·5 to 5·3) of a fermentable saccharoid matter, not removable by lead acetate, in the extract of tumbeki or Persian tobacco (*Nicotiana Persica*). The *nicotine* in this product ranges from 2 to nearly 6 per cent., and the *ash* from 22 to 28 per cent.

H. Müller (*Bied. Centr.*, 1886, p. 409; *Jour. Chem. Soc.*, l. 904) states that fermented tobacco contains, as a rule, little or no starch, and no sugar. The whole of the starch commonly disappears during the first few days of the drying. The sugar thus formed is often converted into water and carbon dioxide, and this change seems to be complete in leaves quickly dried. The last trace of sugar disappears when fermentation sets in, while any residual starch does not appear to be altered.

From the analyses already quoted, it is evident that the proportion of *nicotine* in tobacco varies considerably.[1] According to Schloesing (*Chem. Gazette*, v. 43) dried French tobacco contains from 5 to 8 per cent. of the alkaloid; Virginia and Kentucky, 6 to 7 per cent.; while Maryland and Havana tobaccos contain only about 2 per cent., and ordinary snuff about the same proportion. L. Ricciardi (*Ber.*, xi. 1385) to some extent confirms these results, for he found the nicotine in twenty specimens of tobacco, grown in Italy under various conditions, to range from 5·99 per cent. in a Virginian variety to 1·62 in Havana tobacco.

Tobacco Smoke varies in character according to the proportion of air admitted during combustion, oxidation being necessarily more perfect in the case of a cigar than when the tobacco is smoked in a pipe. In the latter case, a portion of the condensible products is deposited in the liquid state. Tobacco-smoke consists in part of permanent gases, the proportions of carbon dioxide and carbon monoxide in which have been determined by G. Krause. Vohl found sulphuretted hydrogen and hydrocyanic acid, and from 0·7 to 2·8 grammes of ammonia for 100 of tobacco smoked. Vohl and Eulenberg (*Arch. Pharm.*, [2], cxlvi. 130) experimented on the smoke of strong tobacco, burnt both in pipes and in the form of cigars. The smoke was first aspirated through a solution of

[1] According to Ad. Mayer a liberal amount of heat and light, together with sufficient moisture in a rich soil, will not only cause a luxurious development of tobacco plants, but give a large increase in the percentage of nicotine, while the other organic constituents of the plant are not much affected by climatic conditions.

caustic potash, and then through dilute sulphuric acid. The *alkali* absorbed carbon dioxide, sulphuretted hydrogen, hydrocyanic, formic, acetic, propionic, butyric and valeric acids, phenol and creosote; the presence of caproic, caprillic, and succinic acids could *not be ascertained conclusively. The acid absorbed ammonia,* pyridine, C_5H_5N, and all the homologues of the series to viridine, $C_{12}H_{19}N$, inclusive. In addition to the above, carbon monoxide, methane, and several hydrocarbons of the acetylene series were detected. Pyridine was the chief base in the smoke from pipes, while collidine was the prominent base in cigar-smoke.

Vohl and Eulenberg conclude that the nicotine of tobacco is completely decomposed during the process of smoking, and that the intense action of tobacco-smoke on the nervous system is due to the presence of bases of the pyridine series. There is no doubt that some observers have mistaken these bases for nicotine; but Melsens' experiments (*Dingl. Polyt. Jour.*, xlvii. 212) appear to be conclusive as to the presence of nicotine, which he isolated in a condition fit for analysis and to the amount of about 33 grammes for 4½ kiligrammes of tobacco smoked, or about one-seventh of the quantity originally present.[1]

Tobacco Extract varies greatly in strength, and should always be assayed for the proportion of nicotine. A good extract is said to contain about 7 per cent. of the alkaloid. The following analyses by E. Geissler (*Jour. Soc. Chem. Ind.*, viii. 425), of tobacco extract of 40° Baumé, indicate a wide difference in its character, according as it is prepared from the leaves or midribs of the tobacco.

	Liquid.	Mineral Matter.	Containing K_2CO_3	Organic Matter.	Containing Nicotine.
Extract from leaves, .	36·2	15·5	5·0	50·86	8·1
Extract from midribs, .	32·8	22·1	7·73	48·40	1·86

Snuff is manufactured from refuse-tobacco, such as stems, tobacco-smalls, and sweepings. These are moistened with water, subjected to a process of fermentation during six or eight weeks, then ground, mixed with alkaline salts as preservatives, and flavoured as desired. In the United Kingdom, nothing is allowed to be added to snuff

[1] Melsens' conclusion has been endorsed by R. Kissling (*Ding. Polyt. Jour.*, ccxliv. 64), who has collected and reviewed the observations of previous investigators. He considers Vohl's conclusion as to the non-existence of nicotine in tobacco-smoke to be due to that chemist having overlooked the fact that the alkaloid is decomposed by warm caustic potash, a reaction which, if a fact, has certainly not met with general recognition.

but the chlorides, sulphates, and carbonates of potassium and sodium, and the carbonate of ammonium; and any snuff which contains a greater proportion of these salts than 26 per cent. on the dry snuff, including the salts natural to the tobacco, is liable to forfeiture and a penalty of £50. As the proportion of alkaline salts in tobacco-ash varies considerably, it is important that the manufacturer should know the amount present, in order that he may compound a snuff of uniform composition, and not exceed the legal limit. Of the *salts* allowed to be added to snuff, common salt and the carbonates of potassium and ammonium are those most commonly used. In addition, most snuff contains from 25 to 45 per cent. of *water*, and sometimes a considerable quantity of *sand*, the proportion, according to J. Clark (*Jour. Soc. Chem. Ind.*, iii. 554), averaging 5 per cent. on the dry snuff; but ranging from 0·5 to over 10 per cent., and in one case exceeding 30 per cent. A large number of gross and more or less apocryphal adulterants of snuff have been recorded. Among these the sulphides of arsenic, mercury and antimony, chromate of lead, bichromate of potassium, sulphates of copper and iron, alum, lamp-black, ivory-black, cream of tartar, red ochre, brick-dust, and various organic matters find a place. As snuff is neither a "drug" nor an article of food, it is not liable to examination under the Adulteration Acts, and the Excise systematically ignore sophistications which do not affect the revenue. Hence, authentic information respecting the present adulterations of snuff is very limited.

Piturine. $C_{12}H_{16}N_2$.

Piturine, the volatile alkaloid of pituri,[1] was regarded by Petit as identical with nicotine, but its distinct individuality has been established by Liversidge (*Pharm. Jour.*, [3], xi. 815).

In its chemical characters and physiological effects piturine presents the closest resemblance to nicotine, but is distinguished from that base by its reaction with Palm's test. When gently warmed with hydrochloric acid of 1·12 specific gravity, nicotine turns violet, and on addition of a little strong nitric acid the colour changes to a deep orange. Piturine when thus treated does not change colour at all, but when further heat is applied it turns yellow.

Piturine is distinguished from conine by its aqueous solution not becoming turbid on heating, or by the addition of chlorine-water; from aniline it is distinguished by its negative reaction with solution of bleaching powder; and from picoline by being somewhat denser than water. From pyridine, piturine differs by

[1] Pituri consists of the dried leaves of *Duboisia Hopwoodii*, a shrub growing in Australia. It contains from 1 to 2½ per cent. of the alkaloid.

giving a precipitate with cupric sulphate insoluble in excess of the base.

When piturine is treated in ethereal solution with iodine (compare sparteine) the liquid becomes brownish red and turbid, and after a short time deposits yellowish red needles, leaving a yellow mother-liquor. The crystals melt at about 110° C., and dissolve in alcohol with brownish red colour. This solution leaves indistinct needles and oily drops on evaporation; if treated in the cold with caustic soda, an iodoform-like odour is evolved; whereas the iodine-compound of nicotine is said to reproduce nicotine when similarly treated.

Lobeline is the active principle of *Lobelia inflata*, or Indian tobacco, a plant which has received extensive application by unauthorised practitioners, and is also an official drug.[1]

LOBELINE exists in lobelia in combination with a vegetable acid. In presence of certain other constituents of the plant the alkaloid is extremely unstable, being rapidly decomposed on heating an aqueous, or even an alcoholic, infusion of lobelia. In presence of acetic acid the base is more stable, and was obtained by J. W. and C. G. Lloyd (*Pharm. Jour.*, [3], xvii. 1038; xviii. 135) as a colourless, odourless, amorphous substance, permanent in the air, only slightly soluble in water, but readily soluble in alcohol, ether, chloroform, benzene, carbon disulphide, &c. In the pure state lobeline is not hygroscopic, and is but slowly changed on exposure to air. Lobeline turns red with sulphuric acid, yellow with nitric acid, and is precipitated by all the general alkaloidal reagents. The salts, which have not been obtained crystallised, are readily soluble in water, alcohol, and ether. They are described as most violent emetics, a single drop of a tolerably strong solution producing immediate emesis, without disagreeable after-symptoms. The dust is as irritating as veratrine to the nose and air-passages.

[1] The entire dried herb constitutes the official drug, but the dried seeds of lobelia are also largely used. The root of *Lobelia syphilitica* was employed before *L. inflata* was known to medicine, but the root of the latter species does not appear to have been used. According to J. W. and C. G. Lloyd, all parts of lobelia contain the alkaloid, which, however, is most readily obtained from the seeds.

The dust of the plant produces a painful sensation when inhaled. All parts of the herb and seed produce an acrid biting sensation on the tongue, and a sharp, tobacco-like impression on the throat and fauces. Lobelia contracts the pupil, and acts as an expectorant in small doses and an emetic in larger (10 to 20 grains). In poisonous quantities it acts like nicotine, and kills by paralysing the respiration. Several fatal cases of poisoning by lobelia are on record.

INFLATIN was obtained by J. W. and C. G. Lloyd in large colourless, odourless crystals, melting at 225°, insoluble in water or glycerin, but soluble in alcohol, ether, chloroform, benzene, carbon disulphide, and the oil of lobelia, &c. Inflatin is a neutral principle, and appears to have no therapeutic value. The *lobelacrin* of Enders is considered by the Lloyds to be a mixture of inflatin, resin, lobeline, and the fixed oil which lobelia contains in the proportion of about 30 per cent.

No liquid volatile alkaloid could be obtained by Messrs Lloyd from lobelia, by distilling the herb with water, either with or without the addition of caustic alkali, and they considered the supposed volatile base to have been probably a mixture of lobeline, inflatin, and volatile oil.

On the other hand, Paschkis and Smita (*Monatsh.*, xi. 131; *Jour. Soc. Chem. Ind.*, ix. 761) have obtained a volatile alkaloid from *Lobelia inflata*, by extracting the leaves with water acidulated with acetic acid, rendering the concentrated solution alkaline, and agitating with ether. On distilling off the solvent the alkaloid is obtained as a viscous oil, with an odour at once resembling that of honey and tobacco. It is purified by solution in dilute hydrochloric acid, and re-extracted by alkali and ether.[1] After distilling off the ether the base is dried with caustic potash, and distilled in a current of hydrogen. On warming the alkaloid so obtained with a 10 per cent. solution of caustic potash, and gradually adding a 4 per cent. aqueous solution of potassium permanganate, benzoic acid is formed, and can be extracted by filtering off the precipitated oxide of manganese, and agitating the acidulated solution with ether.

The *sulphate* of the above volatile alkaloid, if prepared from lobelia seeds, is obtained in yellow, very hygroscopic granules. When prepared from the leaves, it forms a yellowish white powder, less hygroscopic than the salt from the former source.

According to Dreser, lobeline is the only medicinally active principle contained in *Lobelia inflata*. S. Nunez (*Brit. Med. Jour.*, 1889, 1059) considers it greatly superior to the galenical preparations of lobelia, and recommends it in the treatment of spasmodical asthma and bronchitical dyspnœa.

[1] Up to this point the process of Paschkis and Smita is substantially the same as that of the Lloyd Bros. for the preparation of the non-volatile alkaloid of lobelia. Siebert, by the same process, has recently obtained, both from the herb and seeds of lobelia, a pale yellow alkaline syrup, the crystallised hydrochloride and chloroplatinate of which indicated the formula $C_{18}H_{23}NO_2$ for the free alkaloid.

Sparteine. $C_{15}H_{26}N_2$.

This alkaloid is obtained by Houdé and Laborde (*Pharm. Jour.*, [3], xvi. 543) by exhausting in a displacement-apparatus with proof-spirit the coarsely-powdered leaves and branches of broom (*Spartium scoparium*). The product is filtered, distilled under reduced pressure, the residue dissolved in tartaric acid, the liquid filtered to remove a greenish deposit containing chlorophyll and *scoparin*, $C_{21}H_{22}O_{10}$, the filtrate rendered alkaline by potassium carbonate, and agitated several times with ether. The ethereal solution is shaken with tartaric acid, and the acid liquid separated and again rendered alkaline and extracted with ether, which on evaporation leaves the alkaloid; the yield being about 0·3 per cent. of the plant used.

Sparteine is a colourless, oily liquid, boiling at 287° at the ordinary pressure, or at 180° at 20 mm. It has a somewhat pungent, pyridine-like odour, a very bitter taste, and on exposure to air turns brown and thick. It is soluble in alcohol, ether, and chloroform, but insoluble in petroleum ether. Its solution in alcohol (24 per cent.) has a specific rotation of − 14°·6 for the sodium ray.

Sparteine is a well-defined base, uniting with acids to form crystallisable salts, and having the constitution of a tertiary diamine. The *sulphate* forms large, transparent, very soluble rhombohedra,[1] a solution of which gives with caustic alkalies and ammonia a white precipitate insoluble in excess. Cadmium iodide gives a white curdy precipitate, and sodium phosphomolybdate a white precipitate, dissolving on heating the liquid. Platinum chloride yields a yellow precipitate of $BH_2PtCl_6 + 2aq.$, very insoluble in cold water and alcohol, but crystallising from hydrochloric acid in rhombic prisms. Sparteine gives no coloration with concentrated mineral acids.

When oxidised with potassium permanganate, sparteine yields a

[1] Administered in doses of 0·1 gramme, *Sparteine sulphate* is stated (G. See, *Compt. Rend.*, ci. 1046; *Year-Book Pharm.*, 1886, p. 283) to have a tonic action on the heart more prompt and lasting than that of digitalis or convallamarin, restoring the rhythm of the heart's action better than any known remedy, and resembling belladonna in accelerating the heart-beats in weak and atonic conditions of the heart. It does not appear to have any injurious action on the digestion, or on the nervous system generally.

According to De Rymon, sparteine causes tremor, dilation of the pupils, inco-ordination of movements, and convulsions alternately tonic and clonic.

Schroff found that a drop of sparteine introduced into a rabbit's mouth occasioned spasms of the muscles of the spine and limbs and paralysis of the latter, slowing of the respiration and heart, and death in six minutes.

The effects of sparteine have been compared to those of conine, but they do not explain the value of broom as a diuretic medicine.

small quantity of a volatile (apparently fatty) acid, together with a non-volatile pyridine-carboxylic acid, which on distillation with lime yields pyridine. Heated in sealed tubes with fuming hydriodic acid, sparteine yields methyl iodide and a base containing $C_{14}H_{24}N_2$.

According to Bernheimer, on gradually adding 3 parts of iodine dissolved in ether to an ethereal solution of 1 part of sparteine a black precipitate is formed, which, when separated, washed with ether, and dissolved in boiling alcohol, crystallises on cooling in beautiful green needles containing $C_{15}H_{26}N_2I_3$. This body is insoluble in cold water or alcohol, but dissolves in either liquid when heated. It is insoluble in ether, permanent in the air, and yields free sparteine when heated with caustic alkali (compare "Piturine," page 195). Bromine acts strongly on sparteine at the ordinary temperature, even when largely diluted with ether, forming an undefined resinous mass.

According to Grandval and Valser, when a drop of ammonium sulphydrate is placed on a watch-glass, and a trace of sparteine or one of its salts added to it, a permanent orange-red coloration is immediately produced.

Spigeline is the active principle of *Spigelia Marylandica*, or "pink-root." As obtained by W. L. Dudley by distilling the root with milk of lime it was volatile, gave with iodine a brownish-red precipitate, and with Mayer's reagent a white crystalline precipitate soluble in alcohol and ether, and differing from most similar precipitates by being soluble in dilute acid. Spigeline is said by Stabler to be bitter, precipitated by tannin, and soluble in water and alcohol, but not in ether (?). Pink-root is often used as a vermifuge, and possesses poisonous properties allied to those of gelsemium, depressing the action of the heart and of respiration, and in large doses causing loss of muscular power (*Practitioner*, July 1887; *Amer. Chem. Jour.*, i. 138). It produces strabismus, dilatation of the pupils, and temporary loss of sight, with some drowsiness but not narcotism. A fluid extract of spigelia root is official in the *U.S. Pharmacopœia*.

ACONITE BASES.[1]

The different species of *Aconitum* contain alkaloids of a closely-allied character, but which differ from each other in their chemical

[1] The subjects of this section are discussed at greater length and in more detail than their intrinsic importance seems to warrant, but it appears desir-

composition and physiological activity. The characteristic aconite alkaloids are perhaps the most violent poisons known, but certain species of aconite contain simply harmless, bitter principles. All parts of the plant contain the poison, but the root is richest in alkaloid. If any portion of a poisonous aconite plant be chewed, it will be found to have a taste which may be at first bitterish sweet, but after a time becomes acrid and burning, causing a persistent sense of tingling and numbness of the gums and tongue, which effect lasts for some time and is highly characteristic.

For medicinal use, the German and United States Pharmacopœias admit only the tuberous root of *Aconitum Napellus* (Wolf's-bane or Monk's-hood).[1] The extract of aconite of the British Pharmacopœia is prepared from the fresh leaves and flowering tops of *A. Napellus* ("gathered when about one-third of the flowers are expanded, from plants cultivated in Great Britain"), while the alkaloid (the description of which points to an impure product), the liniment and the tincture are directed to be prepared from the carefully-dried root of the same plant ("collected in winter or early spring before the leaves have appeared, from plants cultivated in Britain or imported in a dried state from Germany").[2] The French Codex authorises the use of the leaf and root of both *A. Napellus* and *A. ferox* possibly

able to present the chemistry of the aconite bases in a more complete form than has been done since the publication of Alder Wright's classical researches ending in 1880. The author is indebted to Dr C. R. Alder Wright for perusal and correction of the article.

[1] The root of *A. Napellus* is from 2 to 4 inches long, and of an irregular conical form. It is much shrivelled longitudinally, and is more or less covered with the scars and bases of broken rootlets. Externally it is coffee-brown, but the transverse section is whitish, and exhibits a central cellular axis with about seven rays. The freshly-cut section rapidly acquires a reddish tint, a character which distinguishes aconite root from horse-radish, which it remotely resembles, and for which it has been fatally mistaken. The details of the structure of aconite root have been minutely described by Richards and Rogers (*Pharm. Jour.*, [3], xix. 912; *Chemist and Druggist*, May 18, 1889), who point out certain differences between the German and British grown roots. The structure of *A. heterophyllum* and Japanese aconite have been described minutely by Wasowicz (*Pharm. Jour.*, [3], x. 301; xi. 149).

[2] Notwithstanding the importance, in the case of such a drug as aconite, of adhering strictly to the directions of the Pharmacopœia, it is stated on the high authority of E. M. Holmes (*Pharm. Jour.*, [3], xx. 900) that aconite-root as met with in commerce is generally of German or Japanese origin, the former being gathered indiscriminately from plants which may vary as widely in properties as *A. heterophyllum* (non-poisonous) and *A. ferox* (highly poisonous), and certainly do vary as much as *A. Napellus* (intensely poisonous) and *A. paniculatum* (non-poisonous).

owing to the widely-spread, but apparently mistaken, impression that the alkaloid known as Morson's aconitine is prepared from the latter species (compare foot-note on page 216).

The roots of aconite plants are not only the richest in total alkaloidal contents, but the alkaloids extracted from the root of *A. Napellus* were found by C. R. Alder Wright to contain a much larger *proportion* of the crystalline base aconitine than the alkaloids from the other parts of the plant (stem, leaves, and flowers).

The various natural alkaloids of the aconites are, broadly speaking, characteristic of particular species of the plant. Thus aconitine is the peculiar alkaloid of *A. Napellus*, pseudaconitine of *A. ferox*, and japaconitine of *A. Fischeri*. It is highly probable that the traces of pseudaconine found by Alder Wright in the alkaloids from *A. Napellus*, and, conversely, the trace of aconitine detected in the bases from *A. ferox*, were due to unsuspected admixtures of other species of aconite in the parcels of roots which professedly came from one species only.[1] Thus, twenty-nine varieties of *A. Napellus* have been described, and some of these exhibited such differences that only an expert could distinguish them from nearly allied species. The true *A. Napellus* flowers in May, and appears to be peculiar in this respect; it is impossible even for a skilled botanist to distinguish the plant by its leaves alone (E. M. Holmes, *Pharm. Jour.*, [3], xii. 736).[2]

The roots of at least two species of Japanese aconite occur in the United States, viz., *Aconitum Fischeri* and *A. uncinatum*. The latter species has been described as poisonous; but, according to V. Coblentz, the root, although it contains an alkaloid, is entirely devoid of the tingling and numbing taste of *A. Napellus*. The physiological experiments of Bartholow on the root of *A. Fischeri* indicate that this plant increases the number and force of the cardiac pulsations, instead of reducing the heart's action like *A. Napellus*. These and other results show that japaconitine and preparations of the Japanese root should by no means be substituted for *A. Napellus* for internal administration (*Pharm. Jour.*, [3], xvi. 545).

Besides the eminently poisonous alkaloids, aconitine, pseudaconitine and japaconitine, characteristic respectively of *Aconitum Napellus*, *A. ferox*, and *A. Fischeri*, other species of aconite

[1] Mandelin, by the examination of *A. Napellus* alkaloids of various degrees of purity, was not able to detect pseudaconitine; and Jürgens also failed.

[2] The root of *Imperatoria Ostruthium*, or masterwort, has been met with as an adulterant of aconite. It resembles aconite tubers in shape, but has an aromatic odour and pungent taste, and the transverse section exhibits numerous oil cells arranged in several circles.

contain alkaloids which appear in some cases to be highly poisonous, and in other cases harmless, bitter tonics. Thus the alkaloid of *Aconitum paniculatum* (which was the official aconite of the *London* and *Dublin Pharmacopœias* of 1836) is an inert, bitter principle, not improbably identical with the *picraconitine* isolated by T. B. Groves from a parcel of roots supposed to be those of *A. Napellus.* The root of *A. heterophyllum* contains a non-poisonous bitter alkaloid, called by its discoverer *atisine;* and it is probable that similar bases occur in other species. *Lyaconitine* and *myoctonine* are physiologically active alkaloids isolated from *A. lycoctonum.* Some species of aconite appear to contain an unisolated base having distinct narcotic properties.

The following table shows the chief sources of the aconite alkaloids and their derived bases. The *root* is the part of the plant referred to in each case :—

PLANT.	Saponifiable Bases.	Basic Products of Saponification.	Unsaponifiable Alkaloids.
Aconitum Napellus. Monk's-hood. Wolf's-bane (blue flowers).	Aconitine.	Aconine.	Amorphous unnamed base.
	Amorphous base.	?	
	Picraconitine (exceptionally present).	Picraconine.	... ...
	Pseudaconitine (very small quantity, if at all).	Pseudaconine.	... ...
Aconitum Ferox. Indian aconite. Nepaul aconite. Himalaya root. "Bikh" or "Bish."	Pseudaconitine.	Pseudaconine.	Amorphous unnamed base.
	Amorphous base (?).	?	
	Aconitine (in very small quantity, if at all).	Aconine.	... ...
Aconitum Anthora (yellowish or white flowers).	Pseudaconitine (?).	Pseudaconine.	... ...
Aconitum Fischeri. Japanese aconite.	Japaconitine.	Japaconine.	Amorphous unnamed base.
	Amorphous base (?).	?	
Aconitum Uncinatum.	Bitter inactive alkaloid.	?	... ...
Aconitum Paniculatum.	Picraconitine (?).	Picraconine (?).	... ...
Aconitum Lycoctonum (yellow flowers).	Lyaconitine.	Lyaconine (Lycoctonine).	... ...
	Myoctonine.	Lyaconine (Lycoctonine).	... ...
Aconitum Heterophyllum (blue or dirty yellow flowers, with purple veins). Atis or Atees root.	?	?	Atisine.

Constitution and Characters of the Aconite Bases.

Much of the earlier work on the alkaloids of the aconites is of little value, owing to the readiness with which the bases

undergo decomposition, and the consequent failure of the observers to obtain them in a pure state.

The following table shows the leading properties of the better known of the aconite bases.

Name.	Synonyms and Sources.	Formula.	Melting-Point, °C.	Appearance and Characters.	Physiologica Effect.
Aconitine, .	Napaconitine. Crystallised aconitine. From *A. Napellus.*	$C_{33}H_{45}NO_{12}$	188	Crystallisable both in free state and as salts. Alkaloid dextro-rotatory. Salts lævo-rotatory.	Intensely poisonous.
Anhydro-aconitine,	Apoaconitine.	$C_{33}H_{43}NO_{11}$	186	Small coherent crystals; crystalline salts.	As poisono as aconitin
Aconine, . .	Saponification of aconitine.	$C_{26}H_{41}NO_{11}$	130	Amorphous; forms amorphous salts. Reduces Fehling's solution.	Bitter; mode ately poiso ous.
Pseudaconitine,	Acraconitine; napelline; feraconitine. From *A. Ferox.*	$C_{36}H_{49}NO_{12}$	105	Base and salts crystallise with difficulty. Saponifiable.	Intensely poisonous.
Pseudaconine, .	Saponification of pseudaconitine.	$C_{27}H_{41}NO_{9}$	100	Amorphous; forms amorphous salts. Does not reduce Fehling's solution.	Bitter; slight poisonous.
Japaconitine, .	Crystalline alkaloid of Japanese aconite root.	$C_{66}H_{88}N_{2}O_{21}$	184-186	Crystallisable; forms crystallisable salts. Saponifiable.	Very poiso ous; close resembles aconitine.
Japaconine, .	Saponification of japaconitine.	$C_{26}H_{41}NO_{9}$	...	Amorphous; forms amorphous salts. Reduces Fehling's solution.	Closely rese bles aconin
Picraconitine, .	Doubtful; perhaps the inactive alkaloid of *A. paniculatum.*	$C_{31}H_{45}NO_{10}$	above 100	Base crystallises with difficulty: but salts easily. Saponifiable.	Bitter; n poisonous.
Picraconine, .	Saponification of picraconitine.	$C_{24}H_{41}NO_{9}$	...	Amorphous.	Bitter; n poisonous.
Lyaconitine, .	From root of *A. lycoctonum.*	$C_{27}H_{34}N_{2}O_{6}$	112-114	Amorphous; dextro-rotatory. Saponifiable.	Poisonous.
Myoctonine, .	With lyaconitine, in *A. lycoctonum.*	$C_{40}H_{56}N_{2}O_{12}$ (?)	144	Amorphous; dextro-rotatory. Saponifiable.	Bitter; pa lytic poiso
Lyaconine, .	Lycoctonine. Saponification of lyaconitine.	$C_{27}H_{47}N_{2}O_{7}$	46	Crystallisable; dextro-rotatory.	Poisonous.
Acolyctine, .	With lyaconine.	... ...	...	White powder.	Paralytic poison.
Atisine, . .	From root of *A. heterophyllum.*	$C_{46}H_{74}N_{2}O_{4}$	85	Forms crystalline haloid salts.	Bitter; n poisonous.

It is not probable that either the foregoing list or that on last page includes all the distinct alkaloidal principles of the aconites. The so-called "amorphous alkaloids" have been very imperfectly

examined, owing to the difficulty of obtaining them in a condition of purity. Of those which have been partially examined, considerable uncertainty exists as to how far they are natural constituents of the original plant, and how far formed by polymerisation or other changes during the process of extraction. T. and H. Smith obtained from the *fresh juice* of the roots of *A. Napellus* an alkaloid which appeared to be narcotine, and which they termed aconelline. The occurrence of this base has not been confirmed, but it is noteworthy that there is a relation in the constitution of narcotine and pseudaconitine; for, while the former yields meconin, $C_{10}H_{10}O_4$, or opianic acid, $C_{10}H_{10}O_5$, on saponification, the latter gives dimethyl-protocatechuic acid. The following formulæ show the constitution of the two last-named bodies.

$$C_6H_2\left\{\begin{array}{l}O.CH_3\\O.CH_3\\CO.OH\\CO.H\end{array}\right. \qquad\qquad C_6H_2\left\{\begin{array}{l}O.CH_3\\O.CH_3\\CO.OH\\H\end{array}\right.$$

Opianic acid. Dimethyl-protocatechuic acid.

The researches of C. R. Alder Wright have demonstrated that the crystallisable alkaloids of *Aconitum Napellus*, *A. ferox*, and *A. Fischeri* (Japanese aconite) are alkyl salts or esters, either of benzoic acid itself or of a derivative of this acid. Thus, when heated with alkalies or mineral acids, or to some extent when heated with water alone, each of the *crystalline* bases undergoes saponification, with formation of benzoic acid, or a derivative thereof, together with a new amorphous base of far less physiological activity than the crystalline alkaloid from which it is derived.[1]

The following table shows the composition of the natural crystallisable alkaloids of the group, and the products of their saponification. The formulæ of aconitine and aconine are those attributed to these bases by Dunstan and Ince (*Jour. Chem. Soc.*, lix. 271), and show H_2 more in the molecule than the formulæ of Alder Wright for the same alkaloids.

[1] The statement made in the text requires qualification. Picraconitine is a saponifiable alkaloid, but is not poisonous. It forms readily crystallisable salts, but the free base has not been obtained crystallised. Atisine, again, is itself amorphous, but forms crystallisable haloid salts, and is not known to be saponifiable. Lyaconitine and myoctonine have not been obtained crystallised, but are saponifiable and yield crystallisable salts.

Crystalline Base.	Products of Hydrolysis.	
	Amorphous Base.	Acid.
Aconitine, $C_{33}H_{45}NO_{12}$	Aconine, $C_{26}H_{41}NO_{11}$	Benzoic acid, $C_7H_6O_2$
Picraconitine, $C_{31}H_{45}NO_{10}$	Picraconine, $C_{24}H_{41}NO_9$	Benzoic acid, $C_7H_6O_2$
Japaconitine, $C_{66}H_{88}N_2O_{21}$	Japaconine, $2C_{26}H_{41}NO_{10}$	Benzoic acid, $2C_7H_6O_2$
Pseudaconitine, $C_{36}H_{49}NO_{12}$	Pseudaconine, $C_{27}H_{41}NO_9$	Veratric acid (dimethyl-protocatechuic acid), $C_9H_{10}O_4$

Lyaconitine, the amorphous alkaloid of *A. lycoctonum*, also yields an acid and one or more bases on saponification (of which one, l y c o c t o n i n e, readily crystallises), but it is doubtful if the reaction can be expressed by any simple formula (see page 223). The amorphous alkaloid myoctonine, from the same source, yields benzoic acid on saponification, together with the crystalline base lycoctonine, and other products.

The saponification of the crystalline aconite bases occurs with a near approach to quantitative accuracy, at least so far as the production of the acid products is concerned; the basic product usually undergoing some further change with formation of a resinous substance. The reaction is best effected by boiling the alkaloid with alcoholic caustic soda for some time, under a reflux condenser. If the product be then acidulated with hydrochloric acid, and agitated with ether, the acid products of the saponification are dissolved. On separating the ethereal solution, and shaking it with soda, the benzoic and veratric acids are dissolved, while resinous matter remains in the ether. On again acidulating the separated alkaline liquid the acids are liberated, and may be dissolved out by agitation with ether. After allowing the washed ethereal solution to evaporate spontaneously, and drying the residue over sulphuric acid, the acids may be weighed; or, where only one is present, the amount may be ascertained by titrating the ethereal solution with standard alkali and phenolphthaleïn. A method adapted for the assay of very small quantities of the aconite bases, and based on this principle, is described on page 234. After weighing, the melting-point of the acid may be ascertained. Benzoic acid melts at 121° C., and may be separated from veratric acid (page 218) by prolonged distillation with water, when only the former body passes over. The distillate may be rendered alkaline, concentrated to a small bulk, acidulated, and the

benzoic acid extracted with ether, and recovered by evaporation of the solution. The veratric acid may be similarly recovered from the liquid left in the retort.

The following table shows the proportions of carbon and hydrogen contained in the crystallisable aconite bases, together with the percentage of gold contained in their aurochlorides (dried at 100°), and the proportion of acid yielded on saponification :—

Alkaloid.	*Formula.*	*Carbon.*	*Hydrogen.*	*Gold in Auro-chloride.*	*Acid by Saponification.*	NaHO *required for Saponification.*
Aconitine, . .	$C_{33}H_{45}NO_{12}$	61·20	6·95	19·96	18·92	6·20
Pseudaconitine, .	$C_{36}H_{49}NO_{12}$	62·88	7·13	19·10	26·49	5·82
Picraconitine, .	$C_{31}H_{45}NO_{10}$	62·95	7·61	21·07	20·60	6·77
Japaconitine, .	$C_{66}H_{88}N_2O_{21}$	63·67	7·07	20·39	19·60	6·43

When the hydrolysis of the natural aconite bases is effected by heating with concentrated mineral acids, or even by water alone under high pressure, the saponification is preceded or accompanied by the removal of the elements of water and a formation of the so-called "apo-bases," preferably called anhydro-bases. The following table shows the relation of the apo- or anhydro-bases to their parent alkaloids, and exhibits the constitutional formulæ of the former :—

Alkaloid.	Anhydro-base.
Aconitine. $C_{26}H_{37}NO_7\left\{\begin{array}{l}OH\\OH\\OH\\O.CO.C_6H_5\end{array}\right.$	**Anhydro-aconitine.** $C_{26}H_{37}NO_7\left\{\begin{array}{l}O\\OH\\O.CO.C_6H_5\end{array}\right.$
Aconine. $C_{26}H_{37}NO_7\left\{\begin{array}{l}OH\\OH\\OH\\OH\end{array}\right.$	**Anhydro-aconine.** $C_{26}H_{37}NO_7\left\{\begin{array}{l}O\\OH\\OH\end{array}\right.$
Pseudaconitine. $C_{27}H_{37}NO_5\left\{\begin{array}{l}OH\\OH\\OH\\O.CO.C_6H_3(OCH_3)_2\end{array}\right.$	**Anhydro-pseudaconitine.** $C_{27}H_{37}NO_5\left\{\begin{array}{l}O\\OH\\O.CO.C_6H_3(OCH_3)_2\end{array}\right.$

Pseudaconine. Anhydro-pseudaconine.

$$C_{27}H_{37}NO_5\left\{\begin{array}{l}OH\\OH\\OH\\OH\end{array}\right. \qquad C_{27}H_{37}NO_5\left\{\begin{array}{l}O\\OH\\OH\end{array}\right.$$

The anhydro-bases are best prepared by heating the parent alkaloids to 100° for six to ten hours with a saturated aqueous solution of tartaric acid. On rendering the liquid alkaline with sodium bicarbonate, and shaking with ether, the anhydro-base is dissolved, and may be obtained in crystals on evaporation of the ethereal solution.

In their physiological effects, the anhydro-bases resemble the alkaloids from which they are derived. Thus "apo-aconitine," or anhydro-aconitine, is extremely poisonous, while anhydro-aconine is nearly inactive.

Japaconitine, the natural alkaloid of Japanese aconite root, undergoes no further change when heated with tartaric acid, for it has the constitution of a sesquianhydro-derivative :—

$$\begin{array}{l}C_{26}H_{39}NO_7\left\{\begin{array}{l}O\\O.CO.C_6H_5\\O\end{array}\right.\\C_{26}H_{39}NO_7\left\{\begin{array}{l}O.CO.C_6H_5\\O\end{array}\right.\end{array}$$

The hydrogen of the OH-groups of the anhydro-bases is capable of replacement by organic acid-radicals. Thus when pseudaconitine is heated to 100° for some hours with a large excess of glacial acetic acid, it loses the elements of water, but the anhydro-base formed is then further acted on with formation of acetyl-anhydro-pseudaconitine, which is a base crystallising (like the parent alkaloid and its anhydro-base) with $1H_2O$, forming a crystalline nitrate and gold salt, and yielding acetic and dimethyl-protocatechuic acids on saponification with alkalies. The same product is obtained if acetic anhydride be used in place of acetic acid; while, if benzoic anhydride be substituted the corresponding benzoyl-derivative is produced. When aconitine is heated with benzoic anhydride it yields, in a similar manner, benzoyl-anhydroaconitine, a product which is apparently identical with that obtained by the action of benzoic anhydride on aconine.

Aconitine, ... $C_{26}H_{37}NO_7\left\{\begin{array}{l}OH\\OH\\OH\\OBz\end{array}\right.$

Anhydroaconitine, . . . $C_{26}H_{37}NO_7\begin{cases}O\\OH\\OBz\end{cases}$

Benzoyl-anhydroaconitine or Dibenzoyl-anhydroaconine, . $C_{26}H_{37}NO_7\begin{cases}O\\OBz\\OBz\end{cases}$

Japaconitine is converted by benzoic anhydride into a derivative containing four benzoyl-groups, $C_{26}H_{39}NO_7(O.Bz)_4$. The fact may be utilised for distinguishing the alkaloid of Japanese aconite from true aconitine as described on page 221.

Aconitine. Napaconitine. Benzoyl-aconine.

$C_{33}H_{45}NO_{12}$; or $C_{26}H_{37}NO_7(OH)_3.O.CO.C_6H_5$.

Aconitine is the crystalline alkaloid of the root of *Aconitum Napellus*, Monk's-hood or Wolf's-bane (French, *Coqueluchon*; German, *Eisenhut*, *Sturmhut*). It exists in combination with aconitic acid, $C_6H_6O_6$ (Vol. I. p. 452).

Aconitine is extremely difficult to obtain in a state of purity, owing to the facility with which it is converted into an anhydro-base, and suffers hydrolysis with formation of the amorphous base aconine, if a mineral acid be employed in its extraction.[1]

Alder Wright found that the whole of the alkaloid could be extracted by alcohol from Japanese aconite root without the addition of any acid; and the same appears to be true of the root of other species of aconite. Thus C. F. Bender (*Pharm. Centralbl.*, xxvi.

[1] One of the best methods of preparing aconitine from aconite root is that of Duquesnel (*Jour. Pharm. et Chimie*, [4], xiv. 94), who exhausts the material in the cold with rectified spirit to which has been added a small amount of tartaric acid. The alcoholic solution is distilled out of contact with the air at a temperature not exceeding 60° C., and the residue diluted with its own measure of water, and filtered from the precipitated resinous and fatty matters. The acid liquid is next agitated with ether or petroleum spirit to remove colouring-matters, and then rendered alkaline with sodium bicarbonate, which precipitates the aconitine and a portion of the amorphous bases, a large portion of the latter remaining in solution. The precipitated alkaloid is extracted by agitation with ether, which, on evaporation or precipitation by petroleum spirit, deposits the base in colourless rhombic tables, which sometimes appear hexagonal in consequence of the modification of the acute angles. The aconitine thus obtained is contaminated by an admixture of amorphous alkaloid, which clings to it with great obstinacy, and cannot be removed simply by crystallisation; but by converting the base into the hydrochloride, or preferably the hydrobromide, recrystallising the salt, and liberating the alkaloid by sodium carbonate, a product is obtained which, when recrystallised from ether, is very pure.

433) has applied extraction by unacidulated alcohol to the preparation of pure aconitine, and the *B.P.* process is based on the same principle. R. Wright (*Pharm. Jour.*, [3], xx. 375) found that chloroform alone did not extract nearly all the alkaloid from aconite root. By first moistening the root with ammonia, drying it carefully, and then percolating with chloroform, T. B. Groves obtained a much better yield than with chloroform alone. John Williams employed amylic alcohol for extracting aconitine.[1]

For the final purification of aconitine, Dunstan and Ince (*Jour. Chem. Soc.*, lix. 271) employed solution of the base in cold dilute hydrochloric acid, and addition of auric chloride in quantity sufficient to precipitate one-fifth of the alkaloid present. The amorphous alkaloid was wholly precipitated, and from the filtrate the pure aconitine was precipitated by sodium carbonate, and when crystallised from ether-alcohol was obtained in large, flat, rhombic prisms with truncated ends, which appeared as hexagonal plates under the microscope.[2] Dunstan and Ince (*Jour. Chem. Soc.*, lix. 271) attribute to the pure aconitine obtained by the above method the composition $C_{33}H_{45}NO_{12}$, which differs by H_2 from the formula of Alder Wright; but the method of combustion on which both formulæ are based is scarcely delicate enough to decide between the two, and as hydrogen-determinations have

[1] The following is an outline of the method of preparing crystallised aconitine ultimately practised by J. Williams (and posthumously published by Richards and Rogers, *Chemist and Druggist*, Feb. 7, 1891), being an improvement on the process previously described by him (*Pharm. Jour.*, [3], xviii. 238):—The aconite root is coarsely ground and macerated in the cold for three or four days with amylic alcohol, which solvent removes both the free base and its salts. The solution is shaken with successive small quantities of water slightly acidulated with sulphuric acid (¼ fluid ounce to the gallon). The last washings should retain a distinct acid reaction, and the liquor should be examined to insure complete extraction of the alkaloid. The acid liquid is then shaken several times with washed ether, to remove amylic alcohol and colouring-matter, and then gently warmed to dissipate the remaining ether. When quite cold the solution is treated with sodium carbonate, and the precipitated alkaloid filtered off, pressed, and dried by exposure to air. When dry, it is boiled for some time with ether (previously washed with water and dried by potassium carbonate), and the solution filtered hot into a basin, when nearly the whole of the alkaloid will crystallise out. The ring of uncrystallisable gummy matter which forms at the edge of the dish can be dissolved by a little *cold* ether, in which the crystals are only sparingly soluble.

[2] The microscopic appearance of aconitine is regarded by Richards and Rogers as the best and most characteristic test of the alkaloid (*Chemist and Druggist*, May 18 1889). Crystallisation is best effected from somewhat dilute alcohol.

notoriously a tendency to be in excess of the truth, the H_{43} formula is quite as probable as the other.

Aconitine is only very sparingly soluble in cold water, requiring 726 parts at the ordinary temperature, according to Jürgens, and nearly ten times this proportion, according to J. C. Umney. In hot water it dissolves more freely, and is soluble in 24 parts of rectified spirit, readily in chloroform and benzene, and moderately in ether; but is almost insoluble in carbon disulphide and petroleum spirit, and is precipitated by the latter from its solution in benzene or ether. It is not extracted from its acidulated solutions by any of these solvents.

Aconitine has a slightly bitter taste, the intensity of which is said to be inversely as its purity. It is extremely poisonous. Solutions, sufficiently dilute to be safely employed, cause a characteristic tingling and numbness of the lips, tongue, and pharynx.[1]

Pure aconitine is stated by Dunstan and Ince to melt at 186°·5 C. (corrected), but Duquesnel gives 140°, Alder Wright 183°–184°, and Jürgens 179°. The material of the earlier observers was probably sensibly impure, but the want of concordance may be due in part to the mode of heating the alkaloid. Thus when slowly heated aconitine melts at a lower temperature than when heated quickly. Dunstan and Ince recommend the use of a bath of paraffin, long enough to entirely immerse the stem of the thermometer. The bath is heated to about 150°, before the thermometer with the thin glass tube containing the alkaloid is immersed, and is kept well stirred throughout the operation.[2]

Aconitine in the free state is dextro-rotatory, a 3 per cent. solution in alcohol having a specific rotatory power of +11°·1 for the sodium ray. On the other hand, the salts are lævo-rotatory, the hydrochloride in aqueous solution showing $S_D = -35°·9$. Similarly

[1] Aconitine is probably the most violent poison known. $\frac{1}{130}$ grain is the ordinary medicinal dose, and $\frac{1}{16}$ grain a fatal dose for an adult. In working with aconitine, great care must be taken to avoid the action of the base and its salts, especially in the solid state. A minute fragment of the dust, too small to be seen, if accidentally blown into the eye, sets up the most painful irritation and lachrymation, lasting some hours; while, if inhaled, a like amount will produce great bronchial irritation or profuse sneezing, and considerable catarrh or sore throat (C. R. Alder Wright).

[2] Alder Wright states that aconitine melts in a capillary tube at 183°–184° (corrected). The final complete melting is preceded by a slight fritting beginning a few degrees below the melting-point, which is lowered by the presence of amorphous bases. With pure aconitine very slight darkening occurs, but it is more marked with impure material.

the crystalline hydrobromide, $C_{33}H_{45}NO_{12}HBr + 2\frac{1}{2}$ aq., gives $S_D = -30°\cdot5$ in 2 per cent. aqueous solution.

SALTS OF ACONITINE.

Aconitine has well-marked basic properties, and forms a series of crystallisable salts. Caustic alkalies, fixed alkaline carbonates and ammonia (but not ammonium carbonate or fixed alkaline bicarbonates), throw down the free base from the solutions of its salts as a white flocculent precipitate, practically insoluble in excess of the reagent.

The salts of aconitine with the mineral acids are neutral to methyl-orange and rosolic acid, but may be titrated with standard caustic alkali and phenolphthaleïn, just as if the acid existed in a free state.

Aconitine Aconitate exists ready-formed in aconite root. It is gummy in appearance, and crystallises with difficulty. It dissolves in water, alcohol, amylic alcohol, and chloroform; and is partially precipitated from its solution in the last menstruum by the addition of ether.

Aconitine Nitrate is readily obtained by dissolving aconitine in dilute nitric acid, and then adding gradually an excess of moderately strong nitric acid, when the salt separates in a bulky form, rendering the mixture semi-solid.[1] When pressed to separate the mother-liquor, and recrystallised from water, it forms rosettes or fine rhombic and short prismatic crystals, which are colourless and transparent, but slightly efflorescent.

The aconitine nitrate thus prepared has a very anomalous composition, containing as it does $B_2(HNO_3)_3$.[2] The *neutral nitrate*, $BHNO_3$, is obtainable as an amorphous residue by evaporating a solution in an equivalent quantity of dilute nitric acid.

Aconitine nitrate is only sparingly soluble in cold water; but

[1] According to J. Williams (*Year-Book Pharm.*, 1886, 433), when aconitine is recovered from the nitrate prepared in this way it crystallises in a different manner from the original alkaloid. This experience is confirmed by Richards and Rogers (*Chemist and Druggist*, May 18, 1889, and Feb. 14, 1891), who attribute a greatly increased physiological activity and slightly reduced melting-point to the alkaloid thus recovered. This interesting result may possibly be due to the partial or complete conversion of the original alkaloid into anhydroaconitine (page 213) by the action of the strong acid employed. If this suggestion be well founded, the anhydroaconitine could be separated as indicated on page 214.

[2] A. Jürgens found crystallised aconitine nitrate, dried at 100°, by titration with caustic alkali and phenolphthaleïn, to contain a proportion of nitric acid corresponding to the sesqui-nitrate (12·71 per cent.), while one-third of this was indicated by rosolic acid (Inaugural Dissertation, Dorpat, 1885).

it dissolves easily in water saturated with carbonic acid, and gradually crystallises as the gas escapes from the liquid.

Aconitine Sulphate is obtained by evaporation of its solution at a gentle heat as a vitreous non-deliquescent mass, which appears under the microscope as a confused mass of crystals.

Aconitine Hydrobromide, $C_{33}H_{45}NO_{12},HBr$, crystallises readily in monoclinic tables containing, according to Jürgens, 2½ aqua.

Aconitine Hydrochloride, $C_{33}H_{45}NO_{12},HCl$, is obtained by slow evaporation of its solution in large rhombic crystals which, according to Jürgens, contain 3 aqua.

Aconitine Aurochloride, $C_{33}H_{45}NO_{12},HAuCl_4$, is thrown down as a yellow amorphous precipitate on adding auric chloride to a solution of aconitine hydrochloride, or to the salt of the alkaloid to which sodium chloride or hydrochloric acid has been added. The precipitate is formed even in very dilute solutions, and is only very sparingly soluble in dilute hydrochloric acid. It dissolves readily in absolute alcohol, methyl alcohol, chloroform, and acetone, but less readily in ether and dilute alcohol. The compound can be crystallised from alcohol, the deposition being facilitated by the cautious addition of water. When pure, aconitine aurochloride melts at 135°·5 (corrected), but a very small proportion of impurity tends to reduce the melting-point to 130°, or less. From a solution of impure aconitine hydrochloride, the impurities are thrown down first, on gradual addition of auric chloride. Dunstan and Ince recommend the preparation of the aurochloride and the determination of its melting-point as a reliable means of identifying aconitine, especially as the pure alkaloid can be readily recovered in a crystalline state from the compound. The only successful method of effecting this, out of a large number tried, was to grind the aurochloride to a fine powder with water, and add sulphuretted hydrogen water, drop by drop, till the gold is wholly precipitated as sulphide. An excess of the reagent should be avoided. The liquid is then filtered, a current of air passed to remove any slight excess of sulphuretted hydrogen, sodium bicarbonate added in slight excess, and the liberated alkaloid extracted by agitation with ether.

On mixing alcoholic solutions of free aconitine and auric chloride, and gradually adding water, aconitine gold chloride, $BAuCl_3$, is precipitated. When recrystallised from alcohol the compound melts at 129°.

CHEMICAL REACTIONS OF ACONITINE.

A solution of iodine in iodide of potassium produces a reddish brown or yellowish amorphous precipitate, even in very dilute (1 : 20,000) acidulated solutions of aconitine. Mayer's reagent

precipitates aconitine solutions, if not more dilute than 1 in 10,000, and may be used for the determination of the alkaloid. Phosphomolybdic acid also precipitates moderately dilute solutions (1 : 5000), and if the aconitine be pure the precipitate dissolves in ammonia without blue coloration. Phosphotungstic acid behaves similarly. Picric acid precipitates solutions which are not too dilute; but mercuric chloride gives no reaction with aconitine solutions much below 1 per cent. in strength; while platinic chloride, and potassium chromate, iodide, ferrocyanide and ferricyanide fail to precipitate aconitine solutions unless very concentrated.

According to A. Jürgens (*Arch. Pharm.*, [3], xxiv. 127, 172) aconitine can be identified under the microscope by dissolving a minute quantity in water acidulated with acetic acid, and adding a particle of potassium iodide. On allowing the solution to evaporate, characteristic crystals of aconitine hydriodide appear, and remain after adding water to dissolve the crystals of potassium iodide simultaneously formed.

An alcoholic solution of aconitine reduces silver nitrate, but no reduction is produced by the salts of aconitine.

A mixture of solutions of potassium ferricyanide and ferric chloride is turned blue by aconitine.

Aconitine, when pure, gives no marked colour-reactions, but as extracted from the tincture and other pharmaceutical preparations, by adding an alkali and agitating with ether, it yields certain colour-reactions which are serviceable as supplementary tests for the aconitine-alkaloids generally (see page 242). The most characteristic property of pure aconitine is its physiological action, which may be supplemented by the reactions with auric chloride, potassium iodide, and the formation of benzoic acid and aconine on saponification.

As tests for the purity of aconitine, Alder Wright recommends the observation of the melting-point, supplemented by the following:—The alkaloid is dissolved in a few drops of dilute acid, pure ether added, and then excess of sodium carbonate solution; the whole being well agitated in a stoppered bottle. The ethereal solution is then separated and allowed to evaporate spontaneously. When only a small volume is left, this is poured away from the deposited crystals, and allowed to evaporate completely. If the aconitine were tolerably pure, the last drops of the ethereal solution will leave a crystalline residue; but if more than minute quantities of amorphous bases be present, these will accumulate in the ethereal mother-liquor, the last portions will leave a varnish or gummy residue on evaporation.

When *strictly pure*, aconitine dissolves without colour in sulphuric

acid; and on adding a few drops of concentrated syrup no red coloration should be produced, even after standing some time.

When heated for some hours to 100° C. with alcohol and caustic soda, aconitine should yield close on 20 per cent. of benzoic acid, determined as on page 234. The resulting acid should melt at 120°, and should not yield any protocatechuic acid on fusion at 250° with caustic potash. This and the other reactions described on page 219 distinguish aconitine from pseudaconitine. From japaconitine, aconitine can be distinguished by its crystalline form, by *careful determination of the carbon and hydrogen* (compare page 204), and by its behaviour with acetic and benzoic anhydrides. In all other characters the two alkaloids closely correspond.

Aconitine is quite unchanged when heated to 100° in a vacuum, and but very slightly altered at 120°. When kept for an hour at its melting-point it loses about 10 per cent. of its weight, and the residue consists wholly of aconine, $C_{35}H_{41}NO_{11}$.

When aconitine is heated with water to 100° for many hours in a sealed tube, it is hydrolysed with formation of aconine and benzoic acid:—$C_{35}H_{45}NO_{12} + H_2O = C_{35}H_{41}NO_{11} + C_7H_6O_2$. The reaction is apt to be incomplete, only 85 per cent. of the base being hydrolysed by heating with water in sealed tube to 140° C. for twenty-four hours. By mere boiling with water under a reflux condenser for a few hours, the alkaloid is practically unchanged. If ammonia be added to the water, a small but appreciable decomposition ensues. Solutions of potassium and sodium carbonates act more powerfully, some hydrolysis occurring even in the cold after prolonged standing, while on boiling nearly complete saponification into aconine and benzoate ensues. Caustic alkalies rapidly effect the same decomposition, especially in alcoholic solution.

When aconitine is heated with a dilute mineral acid (especially hydrochloric acid), the first action consists in the removal of the elements of water with formation of apo- or anhydro-aconitine, $C_{33}H_{43}NO_{11}$. But this dehydration is rapidly succeeded by hydrolysis, and formation of aconine and benzoic acid, just as when alkalies are employed. On the other hand, the weaker organic acids do not effect this hydrolysis, or do so but very imperfectly. Thus aconitine yields no appreciable quantity of benzoic acid when heated to 100° C. for ten hours, with a saturated aqueous solution of tartaric acid; but this treatment effects the complete conversion of the alkaloid into apo- or anhydro-aconitine.

Anhydro-aconitine, $C_{33}H_{43}NO_{11}$, is best obtained by heating aconitine to 100° with a saturated solution of tartaric acid. On evaporating the ethereal solution of the base it is obtained in

small colourless crystals, which cohere and stick to the sides of the glass vessel in a characteristic manner. It melts at 186°·5, *i.e.*, 2° lower than aconitine, and in other respects (including its poisonous properties) closely resembles the parent alkaloid. Anhydro-aconitine forms crystalline salts. The *aurochloride* forms an amorphous precipitate which dissolves in absolute alcohol. If the solution be evaporated *in vacuo* over calcium chloride, the compound $BHAuCl_4$ is deposited in crystals melting at 141°; but if the alcoholic solution be precipitated by gradual addition of water, the crystals deposited melt at 129°, and contain $C_{33}H_{43}NO_{11},HAuCl_4+H_2O$. When this is recrystallised from dilute alcohol it is converted into aconitine aurochloride, $C_{33}H_{45}NO_{12},HAuCl_4$, melting at 135°·5. *Anhydroaconitine gold chloride*, $BAuCl_3$, is obtained by mixing alcoholic or ethereal solutions of the base and auric chloride. It melts at 147°·5, and shows no tendency to pass into the aconitine salt (Dunstan and Ince, *Jour. Chem. Soc.*, lix. 284).

Commercial aconitine is liable to contain the anhydro-base, which may be removed by converting the alkaloid into the hydrobromide, and crystallising the salt from water, when the salt of anhydro-aconitine remains in the mother-liquor.

Aconine, $C_{26}H_{41}NO_{11}$, probably occurs ready-formed in aconite root, and certainly in other parts of the plant. It may be obtained pure by boiling aconitine with alcoholic potash or soda for some hours, distilling off the alcohol, acidulating the liquid with hydrochloric acid, and removing the benzoic acid by agitation with ether. On rendering the solution alkaline, and shaking with chloroform (aconine being reputedly insoluble in ether), the base is taken up.[1] On adding light petroleum gradually to the chloroformic solution the aconine is precipitated. The first portions are impure, but the last fraction is nearly free from colour, though still resinous and friable when dry.

Aconine melts at 130°, is soluble in alcohol and chloroform, and somewhat soluble in water, but is insoluble in anhydrous ether, benzene, and petroleum spirit. Both the free base and its salts resist all attempts to crystallise them. The solutions yield amorphous precipitates with the usual alkaloidal reagents. The *aurochloride*, $BHAuCl_4$, is a pale yellow amorphous precipitate, which is deposited in oleo-resinous films on evaporating its solution in alcohol (Dunstan and Ince, *Jour. Chem. Soc.*, lix. 286).

[1] The author's experience is that if the alkaline liquid be shaken with ether, the greater part of the basic saponification-product (aconine) is extracted, but that a small additional amount of base can be recovered by subsequent agitation with chloroform.

For the isolation of aconine from the mixed alkaloids of *A. Napellus*, the bases are dissolved in dilute acid, excess of potassium bicarbonate added, and the precipitated aconitine filtered off or extracted by ether. The filtrate is slightly acidulated and precipitated by potassio-iodide of mercury, the precipitate separated, suspended in alcohol, and decomposed by sulphuretted hydrogen. On evaporating the filtered liquid, the aconine is obtained as a resin which can be purified by treatment with ether, to remove colouring-matter and other alkaloids, solution in benzene, and precipitation by petroleum spirit. But the product is always amorphous, and yields amorphous salts.

Aconine is very bitter (far more so than aconitine), but does not produce tingling of the gums, and has very little physiological activity ($\frac{1}{300}$ that of aconitine). It is also distinguished from aconitine by its uncrystallisable character, its readier solubility in water and insolubility in ether, and by not yielding benzoic acid when boiled with alcoholic potash or soda. It reduces gold and silver salts at the ordinary temperature and Fehling's solution on heating. It gives a blue coloration when added to mixed solutions of ferric chloride and potassium ferricyanide.

Anhydro-aconine, $C_{26}H_{29}NO_{10}$, is obtained by heating aconine hydrochloride to 140°. The base and salts are amorphous. It is bitter and very feebly poisonous.

AMORPHOUS SAPONIFIABLE BASES OF ACONITUM NAPELLUS.

In addition to aconitine, the active and crystalline alkaloid of *A. Napellus*, and picraconitine, which appears to be occasionally present, indications of the presence of another saponifiable alkaloid have been met with by several observers. Thus Alder Wright and Luff (*Jour. Chem. Soc.*, xxxiii. 318) found that the mother-liquors, from which as much crystalline aconitine as possible had been separated, contained an amorphous base showing C = 66·39, and H = 7·94 per cent., and which gave about 14 per cent. of benzoic acid on saponification. Wright (private communication to the author) states that it is impossible to form any idea of the proportion of the amorphous saponifiable base present, and does not regard his product as a single alkaloid, but believes it still retained aconitine, which was prevented from crystallising by the amorphous bases present. He thinks it probable that the benzoic acid produced on saponification was mainly derived from amorphous saponifiable bases, which may possibly have been in part pre-existent in the plant, but probably were chiefly alteration-products of aconitine, just as the amorphous base quinicine results from the alteration of quinine.

A. Jürgens (Inaugural Dissertation, Dorpat, 1885) has also isolated an amorphous saponifiable base from the root of

A. Napellus, and found it to contain C = 67·74, H = 8·40 per cent., and to yield an unstated proportion of benzoic acid and a base allied to aconine on saponification.[1] BHCl, BHBr, BHI, $B_2H_2SO_4$, $BHNO_3$ and $BH\bar{A}$ were amorphous, but the very small quantity of material at disposal prevented any complete examination of the alkaloid being made. It is probable that the amorphous saponifiable base of *A. Napellus* bears the same relation to aconitine that quinicine bears to quinine, and is a polymeride of the crystallisable alkaloid. Hence the name a c o n i c i n e would appear convenient and appropriate.[2]

J. C. Umney states that the amorphous saponifiable base of *A. Napellus* produced no ill effects on him when taken in 1 grain doses.

Pseudaconitine. Feraconitine. Veratroyl-pseudaconine.

$C_{36}H_{49}NO_{12}$; or $C_{27}H_{37}NO_5(OH)_3.O.CO.C_6H_3(OCH_3)_2$.

Pseudaconitine is the characteristic crystalline alkaloid of *Aconitum ferox*, a native of the Himalayas, and is stated to be also present in *A. anthora*, and other species; also, according to Alder Wright, in small quantity in *A. napellus*.[3]

[1] The remarks made by Mr J o h n C. U m n e y before the British Pharmaceutical Conference of 1891 (*Pharm. Jour.*, [3], xxii. 223, 447; *Chemist and Druggist*, xxxix. 293; *British and Colonial Druggist*, xx. 210) contained various erroneous statements respecting the amorphous, saponifiable alkaloid of *A. napellus*. These statements, the reports of which Mr Umney has declined to correct, conveyed to his auditors the false impression that the recognised proportion of the inactive, saponifiable base in question would suffice to double the proportion of benzoic acid produced on saponification, and hence would invalidate any process of assay based on that reaction (see page 233); whereas the fact is that in no investigation, the results of which have been hitherto published, has the alleged inactive base been obtained free from aconitine, or in the considerable proportion erroneously asserted by Mr Umney, whose mistakes appear to have arisen in part through confusion between the base in question with amorphous unsaponifiable aconite bases.

[2] According to a more recent research by J ü r g e n s (*Pharm. Zeit.*, Sept. 1887), picraconitine has a constitution intermediate between aconitine and aconine. He states that picraconitine results from the splitting off of a single benzoyl-radical from aconitine, while the elimination of two benzoyl-groups results in the formation of aconine; but that in the decomposition of aconitine, not only benzoyl but methyl groups are split off. No detailed account of this suggestive investigation appears to have been published.

[3] "The report that Morson's aconitine is pseudaconitine from Himalaya bikh tubers is now tolerably well disposed of, since Morson has made it known that his aconitine is prepared from the tubers of cultivated *Aconitum Napellus*" (H u s e m a n n, *Pharm. Zeit.*, 1884). At one time, Morson's aconitine was certainly prepared from *A. ferox*.

Pseudaconitine is readily obtained pure by dissolving the mixture of alkaloids isolated from the root of *A. ferox* in dilute nitric acid, and then gradually dropping in strong nitric acid with constant stirring, until, by the separation of the nitrate of pseudaconitine, the liquid becomes thick. It is then drained by means of a filter-pump, and washed slightly with water containing 8 to 10 per cent. of nitric acid. If a perfectly pure salt be required, the product is purified by re-solution in the least possible quantity of hot water, cooling, and dropping in strong nitric acid till the salt crystallises; when it is drained, pressed, and the alkaloid liberated by treating the solution with sodium carbonate. Crystallised pseudaconitine contains $C_{36}H_{49}NO_{12}+H_2O$, but the water of crystallisation is driven off below 100°.[1]

Pseudaconitine presents a close resemblance to aconitine, both in its chemical and physiological characters.[2] It is, however, more soluble in alcohol and ether than the latter base, crystallises with 1 aqua, and melts without darkening at a considerably lower temperature. The melting-point is about 104°–105° C., but is not well marked, fritting occurring a few degrees lower.

When crystallised from ether, or a mixture of ether with petroleum spirit, pseudaconitine forms transparent needles and sandy crystals; but unless the evaporation is extremely gradual the base is apt to separate as a varnish at the upper edge of the solution, and soon forms a milk-white, cauliflower-like, crystalline efflorescence.

Pseudaconitine and its salts (with the exception of the nitrate, BNO_3+3H_2O, and aurochloride) crystallise with difficulty, and the crystallisation is impeded, or wholly prevented, by very small admixtures of amorphous alkaloid or other impurity.

Pseudaconitine Aurochloride, $BHAuCl_4$, is distinctly crystalline when precipitated from a dilute solution. After drying over sulphuric acid it can be readily crystallised from boiling alcohol in minute needles only sparingly soluble in cold alcohol and which are anhydrous when air-dried.

Pseudaconitine Chloroplatinate is soluble with moderate facility in water, and hence is not precipitated except from strong solutions. The *mercuro-iodide*, $BHgI_3$, is amorphous, white, and very sparingly soluble.

[1] Anhydro-pseudaconitine and acetyl-anhydro-pseudaconitine resemble the parent base in crystallising with $1H_2O$.

[2] Pseudaconitine contains a somewhat different proportion of carbon from the other crystalline aconite bases, and the aurochloride contains a somewhat different percentage of gold, but the best defined character of pseudaconitine is its behaviour on saponification.

Pseudaconitine is hydrolysed with great facility. The mere process of heating with dilute alcohol for the purpose of recrystallising it results in the production of a very sensible quantity of veratric acid and pseudaconine (page 219). Hence only a fraction of the alkaloid used crystallises out on cooling, and the mother-liquor yields veratric acid on acidifying, adding water, and shaking with ether. If freshly-precipitated pseudaconitine be boiled with ammonia or sodium carbonate for a few minutes, and the solution then acidulated and shaken with ether, a considerable quantity of veratric acid is dissolved out. When boiled under a reflux condenser for some hours with alcoholic potash, pseudaconitine is entirely converted into veratric acid and pseudaconine or the products of the further decomposition of this base. The proportion of veratric acid obtained approximates closely to the theoretical amount (26·49 per cent.).[1]

By heating pseudaconitine to 100° for some hours with a strong solution of tartaric acid, it is completely converted into anhydropseudaconitine, $C_{36}H_{47}NO_{11}$ (page 205), a base which closely resembles the parent alkaloid.

Veratric Acid, $C_9H_{10}O_4$, or $C_6H_3(OCH_3)_2.COOH$.[1] This body has the constitution of a dimethyl-protocatechuic acid. It melts at 174°–175°, and can be sublimed, but is not volatile with steam. It dissolves in 2100 parts of cold water, and in 160 parts at the boiling-point, and crystallises from a concentrated solution at about 50° in anhydrous needles, while crystals containing 1 aqua are deposited from very dilute solutions at any lower temperature. Veratric acid dissolves in alcohol and ether, and is readily extracted

[1] Possibly pseudaconitine is not the only base contained in *A. ferox* which yields dimethyl-protocatechuic acid on saponification (see Wright and Luff, *Jour. Chem. Soc.*, xxxiii. 174), when preparing pure pseudaconitine nitrate by adding excess of nitric acid to the solution of the crude salt, obtained a nitric acid *mother-liquor* from which no crystals could be obtained. After dilution with water and separation of the precipitated resinous matter, sodium carbonate formed a copious precipitate which was freely soluble in ether, but which could not be made to crystallise or yield a crystalline salt. The base was recovered from ether as a varnish, which on saponification yielded about 19 per cent. of dimethyl-protocatechuic acid, and was not destitute of physiological potency, though it produced far less lip-tingling than pseudaconitine, which can be readily obtained pure by taking advantage of its very slight solubility in a liquid containing 8 to 10 per cent. of nitric acid. Since pure pseudaconitine yields 26½ per cent. of veratric acid on saponification, Alder Wright is of opinion that this amorphous alkaloid probably consisted of about three-fourths of pseudaconitine and other saponifiable bases (possibly alteration-products of pseudaconitine), and one-fourth of non-saponifiable bases; the amorphous bases preventing the crystallisation of whatever pseudaconitine was actually present.

by the latter solvent from its acidulated aqueous solution. It produces no coloration with ferric chloride. When exactly neutralised with ammonia it gives a characteristic gelatinous silver salt on addition of a strong solution of silver nitrate. When veratric acid is fused with caustic potash and a little water at about 250° C., preferably in silver, it yields protocatechuic acid, $C_6H_3(OH)_2.COOH$. If the melt be dissolved in water, the solution acidulated with hydrochloric acid, shaken with ether, and the ether separated and evaporated, the solution of the residual protocatechuic acid in warm water will be coloured an intense bluish green by ferric chloride, the colouring changed to dark red on adding sodium carbonate (compare Part I. page 62). With ferrous sulphate, a neutral solution of a protocatechuate gives a violet coloration.

The formation of protocatechuic acid by fusion with caustic alkali forms a convenient test for pseudaconitine. It is only necessary to fuse the alkaloid with caustic potash and a little water at about 250° in a silver spoon, acidulate the solution of the melt, extract with ether, and test the ethereal residue with ferric chloride.

Other reactions of pseudaconitine dependent on the veratroyl-group are the following:—If a small quantity of the alkaloid and a few drops of fuming nitric acid be evaporated to dryness, a yellow residue is obtained, which gives a beautiful purple-red colour when moistened with a solution of caustic potash in absolute alcohol. If pseudaconitine be heated with concentrated sulphuric acid to 100°, and a drop or two of a solution of vanadium sulphate added, a violet-red coloration is produced.

PSEUDACONINE, $C_{27}H_{41}NO_8$, is contained in the aqueous liquid obtained by saponifying pseudaconitine with alcoholic potash, acidulating, and extracting the veratric acid by agitation with ether. It may be recovered by concentrating the solution, rendering it alkaline by sodium carbonate, and agitating with ether. The base being moderately soluble in water, sodium carbonate produces no precipitate in dilute solutions; and under these circumstances ether extracts the base very imperfectly, but removes certain bye-products, and on subsequently concentrating the alkaline liquid the pseudaconine separates as a resinous mass. The last portions are readily obtained by evaporating the solution to dryness, and treating the residue with ether, while any aconine and colouring-matters soluble in chloroform will be left undissolved.

Pseudaconine is left as a transparent resinous varnish on evaporation of its alcoholic or ethereal solution. On standing a few days the film from ether becomes changed into a mass of crystalline needles; but this effect is prevented by the presence of small

quantities of ether, alcohol, or other foreign matters. If the residue left on evaporating the ethereal solution be moistened with water a portion of the alkaloid dissolves, while the remainder becomes opaque, white and brittle, readily breaking up into particles having a pseudocrystalline appearance. The formation of this apparently crystalline product seems to be peculiar to pseudaconine and lycoctonine.

Pseudaconine dissolves in water to form a solution which is strongly alkaline and very bitter, but it produces no tingling of the skin or lips, and its poisonous properties are very feebly marked. The aqueous solution precipitates silver nitrate, the precipitate being reduced on heating. It also reduces ammonio-nitrate of silver on boiling, but it differs from aconine and japaconine in not reducing hot Fehling's solution, and by its solubility in ether. None of the salts of pseudaconine have been obtained in a crystalline state.

Japaconitine. Sesquianhydro-japaconitine.

$$C_{66}H_{88}N_2O_{21}\text{; or } O\begin{cases} C_{26}H_{29}NO_7 & \begin{cases} O \\ O.CO.C_6H_5 \end{cases} \\ C_{26}H_{29}NO_7 & \begin{cases} O.CO.C_6H_5 \\ O \end{cases} \end{cases}$$

This base is the crystalline alkaloid of Japanese aconite root.[1] It was first isolated by Paul and Kingzett (*Year-Book Pharm.*, 1877, 469), who ascribed to it the formula $C_{29}H_{43}NO_9$. Lubbe believes it to be identical with aconitine from *A. Napellus*, and to have the formula $C_{33}H_{44}NO_{12}$. The formula $C_{66}H_{88}N_2O_{21}$ is due to Wright and Luff (*Jour. Chem. Soc.*, xxxv. 387; *Year-Book Pharm.*, 1878, 490), who showed it to form crystallisable salts, and to be readily saponified with production of benzoic acid. As the alkaloid can be extracted from Japanese aconite root by alcohol alone, without the use of acid of any kind, it seems certain that the base has really the curious constitution attributed to it, or else that the hypothetical parent-base of the formula $C_{33}H_{47}NO_{12}$, or $C_{26}H_{39}NO_7(OH)_3.C_7H_5O_2$, suffers dehydration by the mere process of concentrating its alcoholic solution.

Japaconitine is readily obtained in long rhombic crystals, and

[1] At least two distinct species of aconite are to be met with in the Japanese markets. Much of the root imported to England is said to have been steeped in salt and vinegar, and then dried in wood-ashes and the sun, to protect it against decay and the ravages of insects. In a root so treated, the alkaloid would be liable to be materially modified. (On "Japanese Aconite Root," see *Pharm. Jour.*, [3], x. 149, 1020; xi. 149, 351, 1021, 1041.)

forms a crystallisable nitrate, hydrochloride and hydrobromide. These salts are readily obtained crystalline by adding the dilute acid to a powdered crystal of the alkaloid contained in a watch-glass, and stirring the mixture. Solution to a clear fluid at first takes place, and on further stirring a crystalline magma is formed, just as occurs with aconitine. Japaconitine is dibasic, the salts containing two molecules of acid.

Japaconitine presents the closest resemblance to aconitine, both in its physical and chemical characters. Its melting-point, 184°–186°, differs only by a few degrees from that of aconitine. The proportions of carbon and hydrogen (compare page 205), and the percentage of gold in the aurochloride, are somewhat more tangible distinctions, but not of a very practical character. The crystalline form, as observed under the microscope, is a distinction of value, aconitine appearing in the form of hexagonal plates, and japaconitine in long columnar crystals (see illustrations to a paper by Richards and Rogers, *Chemist and Druggist*, May 18, 1889).

A method of distinguishing japaconitine from aconitine, and even of estimating the proportions of the two bases in a mixture, might be based on the behaviour of the alkaloids with benzoic anhydride. According to Alder Wright, when aconitine is heated to 100° for eight hours, with twice its weight of benzoic anhydride, it is converted into dibenzoyl-anhydro-aconine, $C_{26}H_{37}NO_8(C_7H_5O_2)_2$; whereas japaconitine, when similarly treated, yields a tetra-benzoylated derivative, $C_{26}H_{39}NO_7(C_7H_5O_2)_4$. On adding a minimum of alcohol to the product, and then agitating with aqueous tartaric acid and a large volume of ether, the excess of benzoic anhydride with benzoic acid and certain impurities are dissolved by the ether, while the separated aqueous liquid, when rendered alkaline, yields to ether the benzoylated alkaloids, which can be weighed after evaporating the solvent. On saponifying this product with alcoholic potash (page 204), the aconitine derivative will yield 33·40 per cent. of benzoic acid, while the benzoylated japaconitine will give 50·78 per cent. of the same body.

Japaconitine forms no anhydro-base when heated with aqueous tartaric acid.

Japaconine, $C_{26}H_{41}NO_{10}$, closely resembles aconine (page 214), and can only be distinguished therefrom by elementary analysis.

Picraconitine. $C_{31}H_{45}NO_{10}$.

This base was isolated by T. B. Groves, together with aconitine, from a parcel of German roots purchased in 1874 as those of *A. Napellus*; but it appears doubtful whether there was not a

large admixture of some other species, or whether the roots were not of abnormal character from some peculiarity of soil or climate. It has never been met with again, unless, as is not improbable, the bitter alkaloid of *A. paniculatum* consists of picraconitine. In any case, the possible presence of picraconitine in aconite root must not be ignored; for, while the alkaloid resembles aconitine in yielding benzoic acid on saponification, it does not produce the lip-tingling so characteristic of the latter base, and is practically inert physiologically, half-grain doses having been taken internally without the production of any marked symptoms.

Picraconitine is a bitter, amorphous resin, not fusible at 100°. The dilute solutions of its salts are not precipitated by ammonia, or caustic or carbonated fixed alkaloids, except on the application of heat, when the alkaloid separates as a thick coagulum fusible in boiling water. Picraconitine is soluble in ether and chloroform.

Picraconitine forms crystallisable salts. The *hydrochloride* crystallises readily from hot solutions in fine needles. A moderately strong solution of picraconitine hydrochloride, if saturated with ammonium chloride, becomes turbid on warming from a precipitate of the alkaloidal salt, which, on continuing the heat, is wholly deposited in fine needles. The test is also applicable to the nitrate, and probably to other salts of the alkaloid.

Picraconitine gives no colour-reactions with the usual reagents. Its solutions are precipitated by tannin and Mayer's solution. The *chloroplatinate* is readily soluble, and the *aurochloride* forms a canary-yellow precipitate, not perceptibly crystalline, and exceedingly sparingly soluble in water.

When boiled with alcoholic potash, picraconitine is saponified with formation of benzoic acid and picraconine, $C_{24}H_{41}NO_9$, an amorphous base nearly insoluble in ether, forming amorphous salts, and otherwise presenting the closest resemblance to aconine (compare footnote on page 216).

Lyaconitine and Myoctonine.

The root of *Aconitum lycoctonum*, a species of aconite growing in the Alps and Himalayas, bearing yellow flowers, has been found to contain two alkaloids which differ from the bases isolated from other aconites. So far, the products of the decomposition of these bases by alkalies have not been fully studied, and some obscurity rests on other of their characters.

For the extraction of the bases of *A. lycoctonum*, Dragendorff and Spohn (*Pharm. Jour.*, [3], xv. 104) exhaust the roots with alcohol acidulated with tartaric acid. The tincture is concentrated, mixed with water, filtered, and repeatedly agitated

with ether while still acid. The ether removed traces of an acid resembling protocatechuic acid, but no benzoic acid could be detected. The liquor separated from the ether was treated with sodium bicarbonate and extracted with ether, which removed lyaconitine (1·13 per cent.). Subsequent agitation with chloroform removed the remainder of the lyaconitine, together with myoctonine (0·8 per cent.). The successive treatment with ether and chloroform removed all but traces of alkaloid from the solution. Neither base could be obtained crystallised.

LYACONITINE[1] was obtained, after further purification by ether of the base extracted as above, as a pale yellow resinous substance, yielding a white powder, and completely soluble in dilute acids. After drying *in vacuo*, the base begins to melt at 111°·7, and is completely fused at 114°·8 (corrected), with partial decomposition. It is sparingly soluble in water; very readily in absolute alcohol, chloroform, carbon disulphide and benzene; less readily in ether; and practically insoluble in petroleum spirit. A 10 per cent. solution of the base in alcohol shows a dextro-rotation, $S_D = +31°·5$. An aqueous solution of the nitrate shows $S_D = +19°·4$.

The formula ascribed to lyaconitine by Dragendorff and Spohn is $C_{27}H_{34}N_2O_6 + 2H_2O$.

None of the salts of lyaconitine have been obtained crystallised. The *nitrate* can be obtained and purified by dissolving the base in ether, and cautiously adding nitric acid mixed with ether. The nitrate is precipitated, the first fraction carrying down any colouring-matter contained in the solution.

With strong sulphuric acid, lyaconitine gives a reddish brown coloration, and with syrupy phosphoric acid a violet coloration on warming. When treated with a mixture of 8 c.c. of water, 6 of strong sulphuric acid, and 0·3 of sodium selenate, lyaconitine is coloured a rose or pale reddish violet—a reaction which is not exhibited by the bases from other species of aconite.

Lyaconitine is incompletely precipitated by caustic potash, alkaline carbonates and ammonia. Strong caustic alkalies partially decompose it. Thus, when warmed for a few minutes to a temperature of 35° C. with a 4 per cent. solution of caustic soda, lyaconitine dissolves, and crystalline lyaconine separates from the liquid, and may be extracted by ether. By agitation with chloroform a second base can be extracted, while lycoctonic acid and a resinous substance remain dissolved.[2]

[1] Also called lycaconitine.

[2] Lyaconitine and its salts being amorphous, their composition cannot be considered well-established. The formula attributed to lyaconine is remark-

Lyaconine, $C_{27}H_{47}N_2O_7 + 1\frac{1}{2}$ aqua, is apparently identical with the base described by Hübschmann under the name of *lycoctonine*.[1] It melts at 90°–92°, has an alkaline reaction, and an optical activity of $S_D = +46°·4$. It is very soluble in alcohol and chloroform, less readily in ether and benzene, and dissolves in about 250 parts of water. Its solution has an alkaline reaction, exhibits a fine blue fluorescence, is coloured purple by chlorine-water, and is precipitated by the ordinary alkaloidal reagents.

The aurochloride, platinochloride and nitrate of the base have been prepared.

Acolyctine, a base described by Hübschmann, is probably

able in containing an uneven number of atoms of hydrogen. Correcting it to contain H_{46}, and attributing to lyaconitine the formula $C_{27}H_{30}N_2O_6$, the principal reaction occurring by its reaction with soda would be:—

$$2C_{27}H_{30}N_2O_6 + 2H_2O = C_{27}H_{48}N_2O_7 + C_{27}H_{18}N_2O_7.$$

[1] A specimen of "lycoctonine," from *A. lycoctonum*, presented by Hübschmann to Flückiger, is described by the latter chemist (*Year-Book Pharm.*, 1870, page 99, from *Archiv. der Pharm.*, cxci.) as being crystallised in perfectly white and distinct prisms and needles, melting at 98°–104° without darkening, and forming a transparent glassy mass on cooling. On contact with water this mass at once crystallised. The base was soluble in alcohol, ether, chloroform, amylic alcohol, petroleum spirit and carbon disulphide. By rapid evaporation from these solvents, the alkaloid formed a varnish which crystallised on contact with water; but by slow evaporation crystalline tufts were obtained. The aqueous solution of the base had an alkaline reaction and intensely bitter taste. The physiological effects of lycoctonine were found to differ from those of the other aconite bases both in degree and kind. As a poison, lycoctonine was found much less energetic than aconitine. Mercuric chloride, platinic chloride, phosphomolybdic acid and iodide of potassium produced no precipitate in solutions of lycoctonine salts; but the base was thrown down by tannin, iodised potassium iodide, bromine-water (which gave a precipitate of microscopic needles) and the double iodides of potassium with mercury, bismuth and cadmium. Potassium mercuro-iodide threw down a precipitate which crystallised on standing, In solutions of 1 in 8000 no immediate effect was produced, but in about fifteen minutes beautiful crystals made their appearance; and in a dilution of 1 in 20,000 they were formed in twenty-four hours. The precipitate was readily soluble in alcohol, and crystallised very beautifully from the solution. Mercuro-bromide of potassium does not affect lycoctonine solutions unless very concentrated, but both it and the mercuro-iodide throw down amorphous precipitates from solutions of *aconitine*, and do not affect *narcotine* solutions. With potassio-iodide of bismuth lycoctonine formed a precipitate in a dilution of 1 in 40,000. Sulphuric, nitric and phosphoric acids produced no colour-reactions. The nitrate of lycoctonine crystallised in tables, the sulphate in prisms. Solutions of the salts were not precipitated by caustic or carbonated alkalies, though the base itself was not notably soluble in alkalies.

identical with the second base extracted by Dragendorff and Spohn from the product of the action of caustic alkali on lyaconitine. It is probably a product of the further action of the alkali on lyaconine (lycoctonine). It is described as a white powder, soluble in water, alcohol and chloroform, but insoluble in ether. It forms white precipitates with tannin and lead acetate, and a yellow with auric chloride. Its sulphate forms a white precipitate with ammonium molybdate. Acolyctine produces physiological effects similar to those of myoctonine, but less powerful.

Lycoctonic Acid, $C_{27}H_{18}N_2O_7$, produced by the action of alkalies on lyaconitine (or by heating the base with water or dilute acid in a sealed tube), is crystallisable, and melts at 146°–148°. It is sparingly soluble in water, moderately in ether, and readily in alcohol and chloroform.

Myoctonine, according to Dragendorff and Spohn, has the formula $C_{27}H_{30}N_2O_8+5H_2O$, while Einberg regards it as $C_{40}H_{56}N_2O_{12}+5H_2O$, the water being lost on drying in a current of air at 60°. It is amorphous, has a bitter but not pungent or tingling taste, melts at 143°–144°, and is dextro-rotatory. (S_D for the alkaloid in 10 per cent. solution in alcohol $= +29°\cdot5$; of the nitrate in aqueous solution 21°·2.) It is difficultly soluble in water, but very soluble in alcohol, amylic alcohol, acetic ether, chloroform, benzene, and carbon disulphide. Ether and petroleum spirit only dissolve traces of it. The salts refuse to crystallise. Myoctonine is precipitated by most of the general reagents for alkaloids in solutions not too dilute, and may be titrated by Mayer's solution (1 c.c. = 0·0176 of alkaloid).

An aqueous solution of myoctonine hydrochloride gives with excess of bromine-water an amorphous, very sparingly soluble precipitate, said to contain $C_{40}H_{54}Br_2N_2O_{12}$.

If a fragment of myoctonine be moistened with fuming nitric acid and dried, the residue acquires a reddish brown colour on adding a drop of alcoholic potash (compare atropine).

On heating to 100° with a 4 per cent. solution of soda, myoctonine is stated by Dragendorff and Spohn to behave similarly to lyaconitine, yielding lycoctonic acid, lyaconine, a base resembling acolyctine, and a fourth product of indefinite nature. The behaviour of myoctonine with caustic alkali has also been studied by F. Einberg (Inaugural Dissertation, Dorpat, 1887). When myoctonine was heated on the water-bath with 4 per cent. caustic soda solution, a sparingly soluble basic decomposition-product separated in crystals, which, when filtered off and purified, amounted to 24 per cent. of

the myoctonine taken.[1] The filtrate was brownish, and had a peculiar pungent smell. When acidulated and shaken with ether, a body exhibiting a blue fluorescence was extracted; and on evaporation 30·45 of a brownish semi-crystalline residue was obtained, in which Einberg recognised benzoic acid as the main constituent. The acid liquid, when rendered alkaline with sodium carbonate, yielded 11·84 per cent. to ether and an additional 8·89 per cent. to chloroform, both solvents leaving amorphous yellowish brown residues on evaporation.

According to Salmonowitz, myoctonine is a powerful poison resembling curare in its action, and acting most energetically when introduced directly into the circulation. The subcutaneous injection of 0·075 gramme of the nitrate produced distinct toxic symptoms in cats, and the injection of 0·100 gramme always caused death in about half an hour. Mice were killed in three minutes by a dose of 0·001 gramme.

Atisine. $C_{46}H_{74}N_2O_5$; or perhaps $C_{22}H_{31}NO_2$.[2]

Atisine is the characteristic alkaloid of *Aconitum heterophyllum*, a species of aconite which grows in the more temperate parts of the Himalayas.[3] The atisine exists in the root in combination with aconitic acid.

Atisine is described as white and uncrystallisable, becoming coloured and resinous on exposure to air, and melting at 85°. It

[1] To this base, after drying at 80°, Einberg ascribed the formula $C_{24}H_{38}NO_6$, and considered it identical with Hübschmann's lycoctonine. It melted at 94°, and had a rotation in absolute alcohol of +38°·9. It became amorphous when melted, reassuming the crystalline form on contact with steam. It dissolved in about 250 parts of water, 4 of absolute alcohol, 3·4 of chloroform, 55 of ether, and 63 of benzene, which characters agree with those ascribed by Hübschmann to lycoctonine. The base formed a crystalline nitrate, very hygroscopic and easily soluble in water. Strong sulphuric acid coloured the base bright yellow, changed to a fine orange on warming.

[2] The formula $C_{46}H_{74}N_2O_5$ was deduced by the discoverer of atisine, J. Broughton, from an analysis of the platinum salt. It was confirmed (?) by Wasowicz by carbon and hydrogen determinations on the free base and by analyses, the nature of which are not stated, of the hydriodide, which led to the formula $C_{46}H_{74}N_2O_4,HI+H_2O$ (*sic*). On the other hand, C. R. Alder Wright found that the formula $C_{22}H_{31}NO_2$ agreed better with determinations of carbon, hydrogen, nitrogen and gold in the aurochloride of the base extracted by him from a small batch of Atis roots (*Year-Book Pharm.*, 1879, 422).

[3] *A. heterophyllum* bears flowers which are either wholly blue, or of a dirty yellow with purple stripes. In the bazaars of India the root is sold commonly as a popular bitter tonic, under the name of *Atis* or *Atees root*. The plant and root of *A. heterophyllum* have been fully described and figured by Wasowicz (*Pharm. Jour.*, [3], x. 301, 341, 463). The root is apparently identical with

has a strong, pure, bitter taste, without any acrid or burning after-taste, and is not poisonous. The alkaloid is but little soluble in water or dilute spirit, but readily in strong alcohol, ether and benzene. When the alcoholic solution is strongly diluted with water, the greater part of the alkaloid is precipitated, and the liquid froths strongly on agitation.

According to Wasowicz, strong sulphuric acid colours atisine a faint violet, which changes to red and dirty brown. Nitric acid produces a brown, sulphuric acid a red, and potassium bichromate a green coloration, with a distinct reddish violet zone. Shimoyama (*Pharm. Jour.*, [3], xxvi. 86) obtained with some of the alkaloid prepared by Wasowicz a yellowish solution in concentrated sulphuric acid, gradually changing to a magnificent purple-red, which lasted several days, but became momentarily violet on adding a drop of water. No coloration was produced by nitric or hydrochloric acid. Phosphoric acid dissolved the alkaloid without colour, but on warming the solution for some minutes it began to show a yellowish violet colour. Sulphuric acid and sugar produced at first a yellowish colour, which, after a few minutes, changed to yellowish red and then to carmine-red.

The sulphate, nitrate and acetate of atisine do not appear to crystallise, but the hydrochloride, hydrobromide and hydriodide are crystallisable and sparingly soluble salts.

Ammonia precipitates atisine from the solutions of its salts in white flocks. Tannin gives a yellowish brown precipitate, and potassio-mercuric iodide a white precipitate, dissolving in alcohol to a solution which leaves a distinctly crystalline mass on evaporation.

Atisine Hydriodide, $BHI + H_2O$. When the precipitate of atisine mercuro-iodide is suspended in water, and decomposed by sulphuretted hydrogen, shining pearly scales of atisine hydriodide are deposited. These dissolve in a sufficiency of hot water, and are deposited again on cooling.[1] The salt dissolves in 318 parts of water at 20°, and is very sparingly soluble in alcohol.

Atisine Hydrochloride is a white crystalline powder, more

"wakmah" or "bikmah," the former of which is regarded by Royle as the tuber of the poisonous *A. palmatum*, a view which Shimoyama (*Pharm. Jour.*, [3], xvi. 86) regards as highly improbable. In anatomical characters, wakmah and atis roots exactly correspond, and they yield the same alkaloid.

[1] When the mother-liquor is concentrated to a point at which no more crystals are deposited on cooling, it still yields a precipitate with potassio-iodide of mercury, the alcoholic solution of which leaves an uncrystallisable residue on evaporation. This behaviour appears to point towards the presence of a second alkaloid.

soluble in water than the hydriodide. It has a strong bitter taste, but is free from the disagreeable after-taste of the latter salt.

Assay of Aconite and its Preparations.

The analytical assay and valuation of the alkaloids and other preparations of aconite yield very unsatisfactory results, not so much from the difficulty of isolating and identifying the alkaloids present, as from the uncertainty which exists between the amount and nature of the alkaloids obtained, and the physiological activity of the preparations yielding them. The most conflicting statements have been made respecting the relative activity of the actual alkaloids, even when these have been isolated in a crystalline condition; but the evidence of later observers, especially Mandelin (*Pharm. Jour.*, [3], xvi. 781), tends to show that the experiences of the earlier experimenters were due in part to the use of preparations containing a notable proportion of amorphous and relatively inert bases, to an insufficient number of physiological experiments, and ignorance of the fact that the age, sex, and general condition of an animal, besides its individual idiosyncrasy, materially affects its susceptibility to the poison. Man, again, is evidently more sensitive to aconitine than cats or dogs, and apparently old people are more susceptible than young (compare page 236).

As a means of judging of the quality of aconite root, E. R. Squibb (*Ephemeris*, i. 125) recommends that a thin slice of definite section should be chewed in the lips, and the strength and length of the tingling sensation noted. A. B. Lyons has modified this test by employing one drop of a 10 per cent. tincture of the root. For liquid preparations, Squibb places 1 fluid drachm of a solution of the drug in the anterior part of the mouth, previously rinsed with water, and holds it there for one minute, when the mouth is emptied and again rinsed. A tenth of a minim of a 1 in 1 fluid extract, when examined in this way, should produce a distinct aconite sensation not amounting to tingling, but very suggestive of it, and continuing more or less for fifteen to thirty minutes.

The *total alkaloids* contained in aconite root can be ascertained by processes substantially identical with those employed in preparing aconitine. The details of manipulation to be preferred have been investigated by E. H. Farr and R. Wright (*Pharm. Jour.*, [3], xxi. 1037). They recommend the exhaustion of the root by continuous percolation. One ounce (or 20 grammes) of the drug, reduced to coarse powder, is moistened with spirit of 0·890 specific gravity (which is preferable to either stronger or weaker alcohol), and packed in a conical percolator, when more of the

menstruum is gradually added, and percolation allowed to proceed slowly but continuously until 8 fluid ounces (or 160 c.c.) of percolate has been obtained.

The *tincture* of aconite thus obtained is then evaporated over hot water to a low bulk, till all the alcohol is driven off. The residual liquid is allowed to cool; some water added, if necessary, to reduce the viscosity; and then treated with 15 c.c. of decinormal sulphuric acid. The liquid is then filtered; the precipitate washed with acidulated water; and the filtrate shaken twice with chloroform to remove colouring-matter. The separated chloroform is shaken with acidulated water to remove adherent traces of alkaloid, the aqueous liquid being added to the main quantity. The alkaloidal solution is then treated with a slight excess of potassium carbonate, and the alkaloids extracted by two agitations with chloroform, using 30 to 40 c.c. each time. The separated chloroformic solution is washed with a little distilled water, and then evaporated or distilled over hot water, the residual alkaloids being dried at 100° C. till constant in weight. The alkaloids thus obtained are almost white, and vitreous in appearance. Prolonged exposure at the boiling-point of water causes a slight darkening in colour.[1]

The following proportions of *total alkaloids* were obtained by Farr and Wright by the above process. No. 1 sample was a root of Japanese origin; one sample was of unknown origin; and the rest were roots of *A. Napellus* grown in Germany. The *extractive matter* shown in the table was determined by evaporating a measured quantity of the tincture over hot water, and drying the residue at 100°.

Sample.	From 100 c.c. of Tincture.		From 100 Grammes of Root.
	Alkaloids.	Extract.	Alkaloids.
No. 1 (Japanese),	·073	3·26	·584
No. 2,	·046	2·89	·368
No. 3,	·066	2·92	·528
No. 4,	·050	4·08	·400
No. 5,	·063	3·64	·504
No. 6,	·045	3·18	·360
No. 7,	·070	3·28	·560
No. 8,	·086	1·44	·388
No. 9,	·082	3·40	·656
No. 10,	·050	3·82	·400
No. 11,	·055	2·46	·440
Average,	**·062**	**3·12**	**·496**

These results show a much better yield of total alkaloids than

[1] The foregoing process is, of course, directly applicable to commercial *tincture* and *liniment* of aconite. The *extract* should be treated with alcohol,

was obtained from the root of *A. Napellus* by C. R. Alder Wright, who extracted only ·07 per cent., of which ·03 per cent. was obtained in a distinctly crystalline form.[1] From the root of Japanese aconite, Alder Wright obtained 0·25 per cent. of total alkaloids, of which 0·08 was crystallised. Hager found from 0·05 to 0·40 of crystallisable alkaloid, with a total yield of 0·64 to 1·25 per cent. W. Procter found 0·46 per cent. of total alkaloid in American root (*A. Napellus*), but only 0·20 in root of German growth. From the flowers of *A. paniculatum*, E. L. Cleaver extracted 0·9 per cent. of total alkaloids (bitter, not tingling); from the leaves 0·1 per cent.; and from the extract of the whole plant 0·3 per cent. Richards and Rogers (*Chemist and Druggist*, Feb. 14, 1891) extracted 0·57 per cent. of *crystallised* aconitine from dry Japanese aconite root; 0·14 per cent. from dry root of *A. Napellus*; and 0·71 per cent. from fresh roots (both wild and cultivated) of the same species. These results suggest a notable loss of (crystallisable) alkaloid during the process of drying.

All the foregoing estimations were made by fairly reliable methods, and show that the proportion of alkaloids in aconite varies widely, being probably largely affected by the time of collection, the age of the plant, and possibly by the climate and soil. The method of extraction profoundly affects the nature as well as the amount of alkaloids obtained; any heat or employment of mineral acids tending to effect hydrolysis of the crystalline alkaloids with formation of amorphous bases.

A. B. Lyons found the *moisture* of aconite root to range from 8·2 to 11·2 per cent., and the *extractive* yielded to alcohol to vary from 9·3 to 19·8 per cent. The alkaloid from 10 grammes of the root required from 3·7 to 10·8 c.c. of $\frac{N}{20}$ Mayer's solution for its precipitation.

A striking example of the effect of the process of extraction on the character and proportion of the alkaloids obtained is afforded by the following results of C. Schneider (*Archiv der Pharm.*, ccxix. No. 5), obtained with the same sample of aconite root:—

and the liquid filtered and proceeded with like that percolated from the root. The *ointment* can be treated similarly. The *leaves* and other parts of the aconite *plant* can be assayed in a manner similar to that employed for the root.

[1] A still smaller yield of alkaloid was obtained by Alder Wright and Rennie from the fresh (English) herb (flowers, leaves and stalks), namely, about 0·05 per cent. calculated on the dry herb, and of this only a small fraction could be obtained crystallised (*Year-Book Pharm.*, 1880, 455).

Process Employed.	*Character of Alkaloid.*	*Percentage.*
British Pharmacopœia (1867),	... ...	·002
Morton's, ...	Light yellow powder.	·127
Hirzel's, ...	... ...	·0046
Wittstein's, ...	Well-formed, isolated, six-sided tablets.	·140
Hottot and Liégois', . .	Crystals.	·296
Duquesnel's, ...	Well-developed crystals.	·339

The good results obtained by Duquesnel's process were doubtless due to extraction by percolation with cold alcohol, acidulated with tartaric acid, while all the others employ more or less heat, some with and some without sulphuric acid.

A solution of potassio-iodide of mercury (Mayer's reagent) may be employed for the volumetric determination of aconite alkaloids in acid solution. The difficulty attending the use of the process is the uncertainty of the factor to be employed where there is no knowledge of the composition of the alkaloid present.[1]

Mayer's reagent may be used for the concentration of the aconite bases. The precipitate is filtered off, washed, suspended in water, and decomposed by a stream of sulphuretted hydrogen. The filtered liquid is treated with an alkaline carbonate, and shaken with ether or chloroform; the extracted base being recovered by evaporation in the usual way.[2]

Where the alkaloids of aconite have been extracted and obtained in a fairly pure condition, they may be determined by titration with standard acid and methyl-orange. Operating in the manner described on page 131, the author found that very accurate determinations could be made. Thus 30 milligrammes of crystallised

[1] By titration with Mayer's reagent, Zinoffsky examined the aconites cultivated at Dorpat in 1871. Of the portions of the plants above ground he found the flowers always richest and the stalks poorest in alkaloid; the lowest occupying an intermediate place, and containing, when fresh, about 80 per cent. of water, and from 0·167 to 0·271 per cent. of alkaloid. The highest proportion of alkaloid was 0·729, found in the fresh flowers (collected at the end of July) from *A. Stoerckianum.* By the assay, apparently by Mayer's solution, of entire aconite plants (including the roots) collected at Dorpat Botanical Gardens in June 1871, F. Dragendorff (*Quelques Drogues Actives*) found proportions of alkaloid ranging from 0·054 to 0·327 per cent. in the fresh substance containing about 80 per cent. of water, and from 0·195 to 0·844 calculated on the dry material.

[2] In a private communication to the author, Alder Wright states that there is some reason for supposing that the crystallisable bases are apt to be more or less altered by this treatment, and rendered uncrystallisable.

aconitine was dissolved in 15 c.c. of (neutral) ether; 3 c.c. of water containing a drop of a $\frac{1}{10}$ per cent. solution of methyl-orange (previously rendered sensibly pink by a minute addition of acid) added; and $\frac{N}{50}$ hydrochloric acid dropped in from an accurately divided pipette, shaking well after each addition, till a permanent red coloration of the aqueous layer was obtained. Two experiments made in this manner showed 29·9 and 31·0 milligrammes of aconitine, against 30 taken; while 30 milligrammes of japaconitine (not quite pure) showed 29·8 by titration.

1 c.c. of $\frac{N}{50}$ acid	neutralises	12·94	milligrammes	of aconitine.
,,	,,	10·86	,,	aconine.
,,	,,	14·14	,,	pseudaconitine.
,,	,,	10·46	,,	pseudaconine.
,,	,,	12·44	,,	japaconitine.
,,	,,	10·54	,,	japaconine.

The determination of the total alkaloids of an aconite preparation is in itself of little value if any as a criterion of its activity. It is rather the first step in the process of assay, the potency of the preparation substantially depending on the results subsequently obtained.[1]

[1] Where the amount of material is sufficient it is very desirable to isolate the crystallisable alkaloid; and if this could be effected with an approach to quantitative accuracy, it would probably furnish the most reliable criterion of the physiological activity of the substance. In practice, however, very great difficulties attend such a method of examination. In the first place, there is always a danger that the maximum yield of crystals may not be obtained, and hence that the activity of the preparation will be seriously under-estimated. But, apart from this source of error, there exists the grave difficulty that the amount of substance which is commonly available, or can be conveniently submitted to examination, yields a quantity of total alkaloids far too small to render any method based on crystallisation practically available.

In the *manufacturing laboratory, where comparatively large quantities of* material are available, a good and simple method of effecting at least a partial separation of the crystallisable alkaloids, and which has the advantage of being equally applicable to aconitine, pseudaconitine and japaconitine, is as follows:— The ethereal residue is redissolved in ether in a small beaker. The solution is then stirred with a glass rod which has been dipped in nitric acid, or with a pipette from the orifice of which the acid is allowed to trickle very slowly. At each addition of the acid a white cloud of the alkaloidal nitrate will be produced, which ceases to appear when the acid has been added in excess. After standing a few minutes, all the nitrate formed collects as a crystalline mass on the bottom and sides of the beaker, and the ether may be poured off. The nitrate may be purified by dissolving it in a minimum of hot water, allowing the liquid to become cold, and then adding nitric acid, drop by drop, with constant stirring, until no further separation of crystals takes place.

The only principle of assay hitherto proposed for the aconite alkaloids, making any attempt to discriminate between them and estimate the activity of a mixture, is that based on saponification of the active bases. A method of this kind was suggested by Alder Wright, who proved that the saponification of aconitine, pseudaconitine and japaconitine occurred with a near approach to quantitative accuracy (page 204).

A method of assay based on the saponification of the crystallisable alkaloids of aconite, has the great advantage of distinguishing sharply between the three principal poisonous aconite bases on the one hand, and the comparatively inactive products of their decomposition on the other. As it is generally accepted that aconine has only $\frac{1}{300}$ of the physiological activity of aconitine, and that japaconine and pseudaconine bear a similar relation to their respective parent alkaloids, it may be assumed that the activity of a mixture of aconite alkaloids is substantially represented by the proportion of crystallisable saponifiable base present;[1] and, therefore, the determination of the latter with reasonable accuracy is a considerable advance towards the solution of the problem of the assay of aconite preparations.[2]

The salt is then drained and pressed between filter-paper, dissolved in warm water, sodium bicarbonate added, the liberated alkaloid extracted with ether, the ethereal solution separated and evaporated, and the residue weighed.

[1] It is true that the bitter non-poisonous alkaloid, picraconitine, is saponifiable; but it has only been met with on one occasion (1874, see page 221), unless it is identical with the imperfectly-examined bitter alkaloid obtained by E. L. Cleaver from the root of *A. paniculatum.* Lyaconitine and myoctonine, the amorphous alkaloids of *A. lycoctonum*, are saponifiable, but are of no practical interest. Both Alder Wright and A. Jürgens found a small quantity of an amorphous saponifiable alkaloid in *A. Napellus*, and J. C. Umney has stated that unpublished experiments of his confirm this conclusion. But neither Wright nor Jürgens succeeded in preparing the base in question quite free from aconitine, and the quantity isolated was too small to allow of complete examination. How far these little-known bodies have a practical bearing on the saponification-process of assay is uncertain, and hence the results must be regarded as tentative, except where the method is applied to the alkaloid previously obtained in a crystallised state.

[2] Alder Wright holds strongly that all galenical preparations of aconite and amorphous alkaloids should be abandoned, and only well-crystallised alkaloids or their salts employed.

It is a grave scandal that, although the enormous difference in physiological potency between the crystalline alkaloids of the aconites and the amorphous bases associated with them, or produced by their decomposition, has been long recognised, and become generally known, and while crystalline aconitine can be readily prepared, that a preparation should still be sold under the name of "aconitine" which is not crystallised, and contains a large proportion of

Alder Wright's saponification experiments were made on comparatively large quantities of the alkaloids; but to be of any practical value the method of assay must be available with a quantity of aconite bases not exceeding 50 milligrammes, and should even be applicable with half that quantity. The author has succeeded in making very satisfactory determinations on these small quantities by the following method of operating, which may be conveniently applied either to an ether or chloroform residue, or to the liquid resulting from the titration of either of these with standard acid and methyl-orange, as already described. The residue or solution, containing 30 to 80 milligrammes of alkaloid, is treated with 20 c.c. of rectified spirit (neutral to phenolphthaleïn) and 3 c.c. of a solution of caustic soda in an equal weight of water. The liquid is then boiled for an hour in a flask under a reflux condenser, after which the alcohol is distilled off, and the residual liquid acidulated with hydrochloric acid. The liberated benzoic or veratric acid is extracted by agitation with about 15 c.c. of ether, and the ethereal solution separated and washed with successive small quantities of water, until the washings show their freedom from mineral acid by ceasing to redden litmus. The ethereal liquid is then separated and transferred to a small stoppered cylinder (25 c.c. capacity); about 5 c.c. of water faintly coloured with phenolphthaleïn added; and $\frac{1}{50}$ normal baryta-water dropped in from a finely-divided pipette until the aqueous layer acquires a pink colour, which is not destroyed by agitation with the ethereal stratum.

From the volume of standard baryta consumed, the amount of aromatic acid resulting from the saponification can be calculated. One c.c. of $\frac{N}{50}$ baryta neutralises 2·44 milligrammes of benzoic acid, or 3·64 milligrammes of veratric (dimethyl-protocatechuic) acid. Although these acids have different combining weights, the volumes of alkali neutralised by equivalent weights of them are, of course, identical; and hence no grave difference results in calculating the saponifiable alkaloid, whether benzoic or veratric acid has been produced by the saponification. Thus:—

1 c.c. of $\frac{N}{50}$ baryta represents 12·94 milligrammes of aconitine saponified.
" " 14·14 " pseudaconitine saponified.
" " 12·44 " japaconitine saponified.

In three experiments, where a weight of 30 milligrammes of the

practically inactive base. It is a question whether the sale of such an impure preparation as "aconitine" is not an infringement of the Sale of Food and Drugs Act, notwithstanding that the *British Pharmacopœia* officially recognises the indefinite mixture as "aconitine," and describes it as "usually amorphous."

same sample of crystallised aconitine was saponified, the baryta solution used represented 31·6, 28·3 and 30·9 of the alkaloid. In the case of japaconitine (not quite pure) the process indicated 29·8, against 30 milligrammes taken.

If desired, the titration being completed, hydrochloric acid may be added, when the aromatic acid will be liberated and redissolved by the ether. On separating this solution and allowing it to evaporate spontaneously, the weight of the acid may be ascertained and its melting-point observed; or the ether may be separated from the aqueous liquid, and the latter acidulated, largely diluted and distilled, when a separation of the benzoic and veratric acids will be effected, the former volatilising with the steam and the latter remaining in the retort. This difference of behaviour enables pseudaconitine to be recognised and estimated in presence of aconitine and japaconitine.

By the foregoing method of assaying the mixed alkaloids from the tincture of *A. Napellus* root,[1] G. E. Scott-Smith obtained in the author's laboratory the following results:—

	A.	*B.*	*C.*	*D.*	*E.*	*F.*	*G.*	*H.*
Weight taken, in milligrammes,	55·0	51·7	21·9	87·0	21·0	31·5	17·2	23·5
Alkaloid by titration (in terms of aconitine),	69·0	66·7	29·4	...	28·8	...	18·1	24·9
Benzoic acid,	5·2	4·0	...	8·4	...	4·8	4·1 (G. and H.)	
=Aconitine,	27·7	20·4	...	44·5	...	25·7	22·1 (G. and H.)	
Percentage of saponifiable alkaloid,	50·4	39·5	...	51·1	...	81·6	56·1 (G. and H.)	

If desired, the basic product of the saponification can be isolated by rendering the liquid alkaline with sodium carbonate or caustic soda, and agitating with ether or chloroform. The latter solvent extracts a trifling further quantity from the liquid which has already been treated with ether. The few experiments made in this direction in the author's laboratory gave somewhat erratic results, probably owing to the imperfect extraction of the bases by immiscible solvents, and the further action of the caustic alkali on them.

[1] The alkaloids from a tincture prepared from the root of *A. ferox* gave, for 76·7 milligrammes taken:—By titration, 74·9 of alkaloid, calculated as pseudaconitine; saponified, 14·3 milligrammes of veratric acid by titration, against a weight of 13·0 extracted by ether. The former result represents 55·1 of pseudaconitine, leaving 21·6 of unsaponifiable alkaloid. The basic product of the saponification extracted by ether, followed by chloroform, from the alkaline residue, amounted to 18·5 milligrammes, and neutralised acid equivalent to 51·4 of pseudaconine, or 69·4 of pseudaconitine.

Toxicology of Aconite.

Aconitine is one of the most violent poisons known, and pseudaconitine appears to be fully as active; whereas picraconitine, atesine, and some others of the natural alkaloids of the aconites appear to be harmless bitter principles. The bases produced by the saponification of the poisonous alkaloids are also comparatively inert ($\frac{1}{300}$ of the toxicity of aconitine), and it is probably to the presence of these and other relatively inactive bodies, in variable proportion, in the so-called "aconitine" of commerce that the notorious uncertainty in the activity of that preparation is largely due. Some of the recorded variations verge on the fabulous, and are probably in some measure due to the experiments being insufficient in number, and made without due regard to the difference in susceptibility to the poison caused by age, sex, and general condition of the animals operated on.[1] A more reliable preparation is obtainable since the conditions and importance of obtaining crystallised aconitine, and of preparing the base from certain definite species of aconite, have become more generally recognised.[2] From certain

[1] K. F. Mandelin states (*Pharm. Jour.*, [3], xvi. 781), as the result of very numerous experiments both on frogs and warm-blooded animals, that not only do animals of different species behave dissimilarly, but even with animals of the same species a considerable difference can frequently be observed in respect to the lethal dose, according to the age and condition of nourishment. With frogs, in particular, considerable differences are observable; and female frogs are more susceptible to the poison than males. Old animals are more susceptible than young ones; and the symptoms may vary according to the individuality and nourishment of the animals experimented on.

[2] Some interesting results of the action on sparrows of the principal makes of aconitine prepared in 1872 have been described by H. Duquesnel (*Year-Book Pharm.*, 1872, page 241). Administered by subcutaneous injection, in a dose of 0·0005 gramme in 10 drops of slightly acidulated water, crystallised aconitine produced death in 1 minute; the alkaloid of the *French Codex* (Hottot's preparation), in 15 minutes; Merck's aconitine, in 75 minutes; French commercial aconitine, in 120 minutes; and Hübschmann's napelline (probably impure aconine), profound sleep, not followed by death. Hottot's aconitine is described as amorphous, white, pulverulent, containing 20 per cent. of water, fusible at 80°, and assuming after loss of water a resinous transparent appearance, but not forming crystallisable salts.

P. C. Plugge (*Archiv der Pharm.*, Jan. 1882) was led to investigate the relative toxicity of commercial "aconitines" in consequence of a death from the accidental dispensing of Petit's preparation, instead of Friedländer's, which was intended but not specified by the prescriber. Plugge found the relative activities to be, Petit's nitrate of aconitine, 170; Merck's nitrate of aconitine, 20 to 30; Friedländer's aconitine, 1. He placed the various commercial specimens in the following order, commencing with the strongest:—

observations of Richards and Rogers (*Chemist and Druggist*, Feb. 7 and 14, 1891), it is not improbable that commercial crystallised aconitine sometimes contains a large admixture of anhydro-aconitine, and that this base is considerably more active than the parent alkaloid (A. H. Allen, *Pharm. Jour.*, [3], xxii.).

The poisonous effects of aconite and its preparations appear to be entirely due to the characteristic alkaloids contained therein,[1] and are generally assumed to be substantially the same in kind and degree, whether aconitine itself, or one of its analogues, pseudaconitine or japaconitine, be the base present.[2] This, however, is by no means certain.

Petit's, Morson's, Hottot's, Hopkins and Williams', Merck's, Schuchardt's, Friedländer's.

E. R. Squibb (*Ephemeris*, i. 135) in 1882 classified the four chief makes of aconitine as follows:—Duquesnel's crystallised aconitine, 111; Merck's "aconitine" from Himalaya root (pseudaconitine), 83; Merck's ordinary aconitine, 8; aconitine of unknown make, 1; powdered aconite root, 1.

F. A. Thompson, by employing Squibb's physiological test, classified various samples of commercial aconitine as follows:—Gehe's crystals, 480; Merck's, 350; Duquesnel's, 300; Gehe's amorphous alkaloid, 90 to 45.

Buntzen and Madsen (*Pharm. Jour.*, [3], xvi. 366) concluded from experiments on frogs that Gehe's amorphous aconite was the most powerful of the specimens examined. Next came some preparations made from Vosges roots; then the crystalline preparations of Gehe, Petit, and Merck; and afterwards preparations by Madsen from Swiss roots. Duquesnel's aconitine gave far less effective results than other observers have stated. Great differences were observed in samples of alkaloid from Japanese roots, while that from bish root (pseudaconitine) was inferior in quality, though this may have been due to the roots having been submitted to the action of heat.

[1] H. Duquesnel found that an alcoholic extract of aconite root, from which the alkaloid had been removed in the ordinary way by agitating the alkaline solution with ether, when administered to birds produced a sound sleep of several hours, without anæsthesia, followed by complete recovery. Larger doses were fatal. The extract employed by Duquesnel probably contained aconine, which is imperfectly extracted by ether. Hübschmann's "napelline," which was probably impure aconine, produced similar symptoms. Duquesnel's extract would also contain aconitic acid, which Fleming found to have but little effect when administered to rabbits hypodermically. Torsellini, however, found aconitic acid to have a paralysing effect on the heart of a frog.

[2] Mandelin (*Pharm. Jour.*, [3], xvi. 782) disputes the statement of Langgaard, that japaconitine is "one of the strongest of poisons, which exceeds aconitine and pseudaconitine in activity." He even doubts the chemical difference between aconitine and japaconitine, and finds in both cases the lethal dose for frogs to range from 1·2 to 2·4 milligrammes per kilogramme of body weight; for guinea-pigs, 0·05 milligramme; and for dogs and cats, 0·06 to 0·075 milligramme per 1000 grammes.

Poisoning of human beings by pure aconitine has been of comparatively rare occurrence; but there have been numerous cases of poisoning by the roots, leaves, and galenical preparations of aconite, the greater number being the result of accident.[1] The root has been occasionally eaten in mistake for horse-radish, which it somewhat resembles (compare page 199).

The medicinal dose of the *B.P. tincture* of aconite is from 5 to 15 minims. A. Wynter Blyth considers twice the maximum dose, or 30 minims, likely to be fatal to an adult, though the least fatal dose is usually stated at above twice this measure. *Fleming's tincture* of aconite is from three to six times the strength of the *B.P.* preparation.[2] The *B.P. liniment* is eight times as strong as the tincture.[3] The fatal dose of *aconitine* is difficult to fix, as in the few cases in which a fatal dose of the pure alkaloid has been administered the quantity taken has not been known; and in the cases of poisoning by preparations of aconite there is the greatest uncertainty as to the amount of alkaloid contained therein. Headland considers $\frac{1}{10}$ grain of aconitine an ordinary fatal dose for an adult, and $\frac{1}{16}$ grain of the nitrate has actually caused death. Death appears to have been caused in one hour by 0·0005 gramme of aconitine (*Pharm. Jour.*, [3], xx. 734). Wynter Blyth considers ·002 gramme or ·03 grain the minimum fatal dose for an adult, when the poison is taken by the mouth; but that if given hypodermically, 0·0015 gramme would probably kill, since the whole of the poison is then thrown on the circulation at one time, and there is no chance of its elimination by vomiting. Pereira relates a case in which $\frac{1}{50}$ grain nearly proved fatal to an elderly lady. Recovery has occurred after taking $2\frac{1}{2}$ grains, but in this case there was violent vomiting immediately, and most dangerous

[1] A. Wynter Blyth, in his work on *Poisons*, states that he had collected from European literature, of the ten years prior to 1874, eighty-seven cases of poisoning by aconite in some form or other. In these were two cases of murder, seven of suicide, and seventy-seven more or less accidental. Six of the cases were from the use of the alkaloid itself; ten from the root; in two cases children eat the flowers; in one case the leaves of the plant were cooked and eaten by mistake; in seven the tincture was mistaken for sherry, brandy, or liqueur; and the remainder were caused by the tincture, the liniment, or the extract.

[2] Dr Male, of Birmingham, died from the effects of 80 drops of Fleming's tincture, taken in ten doses of 8 drops each, in the course of four days.

[3] Dr C. Vachell, of Cardiff, has published a case of fatal poisoning by 2 grains of *extract* of aconite taken in pills. This was the maximum dose of extract according to the *British Pharmacopœia* of 1867, but in the edition of 1885 the dose is stated at $\frac{1}{4}$ to 1 grain.

symptoms for thirty hours.[1] In the Lamson case (*Guy's Hospital Reports*, 1883, page 307) the victim probably received about 2 grains.[2]

The symptoms of aconite poisoning usually begin to manifest themselves a few minutes after the poison is taken, and are, in some respects, quite peculiar and characteristic. They usually, but not invariably, commence with a tingling and numbness of the lips, tongue, gums, and throat, accompanied with a burning sensation in the stomach. These effects are succeeded by tingling and creeping sensations in various parts of the body, pains in the abdomen, headache, vertigo, and nausea, frequently accompanied by vomiting and sometimes by purging. There is, also, diminished sensibility of the skin, constriction in the throat, frothing at the mouth, partial or entire loss of voice, impaired vision, ringing in the ears, and feeling of tightness in various parts of the body; muscular tremors, cold perspirations, loss of muscular power, and great prostration generally. Sometimes there is alternate contraction and dilation of the pupil.

The most constant symptoms of aconite poisoning are difficulty in breathing, progressive muscular weakness, a weak intermittent pulse, and, in most cases, vomiting, especially when the poison has been taken by the mouth, instead of subcutaneously. Death usually occurs from syncope, preceded in some cases by delirium and convulsions. Convulsions occurred in ten cases out of ninety-four collected by Drs Tucker and Reichert,[3] and opisthotonos happens

[1] In a case of poisoning by aconite an emetic should be at once given, or the stomach-pump promptly used. Stimulants may be given with advantage. Animal charcoal, to be afterwards removed by the stomach-pump, has been recommended. Strychnine and digitalis have been used successfully as antidotes, and a solution of iodised iodide of potassium has been suggested.

[2] In 1881, a medical man named Lamson gave his brother-in-law, P. M. John, a youth of 19, paralysed below the pelvis, a dose of Morson's aconitine, contained in a gelatin capsule. Some twenty or thirty minutes after, John was seized with pain in the stomach, which he at first called heartburn. He then vomited, and suffered great pain, complained of the skin of his face being drawn, of a sense of constriction in the throat, and of being unable to swallow. He retched violently, and vomited a small quantity of dark brown fluid. Injections of morphine gave some relief, but the symptoms returned, and he was with difficulty kept down by two men. Death occurred four hours after administration of the poison, and the victim was conscious almost to the last.

[3] These symptoms probably depend largely on the dose taken. With large doses, the heart's action is arrested before the poison has had time to materially affect the excitability of the motor nerves, and the heart once stopped, further absorption is diminished or arrested.

occasionally. Death from aconite poisoning commonly ensues in from two to six hours, though there is considerable variation in this respect.[1]

The post-mortem appearances from aconite poisoning are by no means characteristic. They are congestion of the lungs and liver, with an injected condition of the brain and its membranes. There is more or less redness of the stomach and intestines, which are frequently found empty. Great redness of the stomach and intestines is sometimes the only abnormal appearance after aconite poisoning, and this does not occur when the poison has been given hypodermically. The right side of the heart usually contains more or less blood, and the blood throughout the body is generally fluid and dark in colour.[2]

TOXICOLOGICAL DETECTION OF ACONITE.

In any case of suspected poisoning by aconite or its preparations, the symptoms presented before and after death are of the utmost importance.[3] The poison is so violent, so readily decomposed, and so wanting in delicate and characteristic chemical reactions, that there is but little hope of detecting it in the body by chemical analysis. With care, however, this may sometimes be effected, and if the chemical reactions be distinctly confirmed by a physiological test, the presence of the poison may be considered definitely proved. The aconite alkaloids have been recovered from the urine, the blood, and the liver, and have been detected in the stomach several months after death; but the poison has been destroyed in cases where the viscera have become and remained alkaline for some time from putrefactive decomposition.

In cases of supposed poisoning by aconite, the stomach and intestines should be carefully examined for portions of the leaves or other parts of the plant; which, if found, may be identified by

[1] In five cases of aconite poisoning recorded by J. W. Mallet, death ensued respectively in 8, 10, 15, 75, and 135 minutes, while in a sixth case it did not occur till four days after the poison was taken.

[2] In the Lamson case, sixty-four hours after death, there was great redness and inflammation of the cardiac end of the stomach, which had a blistered appearance, the mucous membrane showing in places small, slightly raised, yellowish grey patches. The duodenum was greatly congested, and there were congested patches in other parts of the small intestine. The brain and its membranes were slightly congested, and the lungs much so, especially towards the posterior parts. The heart was very flaccid, nearly empty, and stained with blood-pigment. The pupils were dilated, and the lips and tongue pale. The bladder contained three or four ounces of urine.

[3] It is for this reason that the symptoms of aconite poisoning are described in the text at greater length than would appear necessary in a work treating of the chemist's duties rather than those of the medical practitioner.

comparison of their botanical characters with those of real aconite. The fragments may be washed with a little distilled water, and masticated with the front teeth, when the persistent tingling and numbness so characteristic of aconite will be distinctly recognisable.

For the isolation of aconite bases in cases of poisoning, the suspected matters should be finely divided and treated at the ordinary temperature with strong alcohol, which should be slightly acidulated with tartaric acid, unless already distinctly acid. The liquid is strained and evaporated to a low bulk at a temperature not exceeding 40° C. The residual liquid is filtered cold, acidulated with tartaric acid, if requisite, shaken with ether, separated, and rendered alkaline with sodium carbonate. The alkaloids are then extracted by agitation with ether or ether-chloroform, the solution washed by agitation with water, and evaporated at a gentle heat.

The alkaloidal residue having been obtained, it should be dissolved in a few drops of water acidulated with acetic acid, and a drop of the solution placed on the tip of the tongue or inside the lower lip. E. R. Squibb recommends that the quantity to be tasted should be dissolved in about 60 drops of water, which is then held in the front part of the mouth (previously rinsed) for one minute, and then discharged. Another good plan is to drop the solution on a fragment of porous biscuit, which is then chewed with the front teeth. If any aconitine or other poisonous aconite base be present it will produce, in a period of time not exceeding fifteen minutes, a marked tingling sensation of the tongue and lips (somewhat similar to the effect produced by scalding the tongue with hot tea); and, if the quantity be sufficient and the liquid has reached the tonsils a distinct sensation of sore throat will be observed. These effects last for a considerable time, and are produced in a most marked and unmistakable manner by a single drop of the *B.P.* tincture of aconite, corresponding to $\frac{1}{8}$ grain of the root, and probably not more than $\frac{1}{1600}$ grain of total alkaloids. The effect is so characteristic and delicate that it constitutes by far the best test for the presence of the poison. If not produced it is practically useless to apply other tests, as, in the absence of the physiological reaction they would at least be inconclusive; but, having obtained the characteristic tingling sensation, the chemical tests often afford useful confirmation, and enable the analyst to form an opinion as to whether pure aconitine or a galenical preparation of the aconite plant was taken.[1]

[1] An interesting case of this kind has occurred in the author's personal experience. A man of suicidal tendencies was suddenly taken violently ill at a country inn. He suffered from difficulty of respiration and inability to use his limbs, especially on one side, had violent convulsions, and died before

The chemical tests should be applied to single drops of the acidulated solution placed on microscope-slides; or, in the case of the colour-tests, to the residues left on evaporating a few drops at a gentle heat on the inside of a porcelain crucible cover (compare page 145). The reactions which may prove of service are:—

1. The formation of a crystalline nitrate on adding a small drop of nitric acid at the end of a glass rod (page 210).

2. The formation of a crystalline aurochloride on adding a drop of auric chloride (page 211).

3. The formation of crystals of aconitine hydriodide on adding a minute fragment of potassium iodide, and allowing the solution to evaporate (page 212).

4. On adding cold concentrated sulphuric acid to the aconite residue *no reaction is produced immediately*, but very gradually, or more rapidly on cautiously warming, a deep brown coloration is produced, passing through various shades of reddish brown to violet. The reaction is not produced by pure aconitine.

5. In presence of certain impurities, which adhere tenaciously, aconite bases develop a well-marked cherry-red coloration, changing to crimson, when treated with sugar and sulphuric acid in the manner described under morphine. The mixture of bases extracted from aconite root in the ordinary process of assay gives this reaction very distinctly.

6. Impure residues of aconite bases, when treated with syrupy phosphoric acid, give a violet coloration when the mixture is heated for some time on the water-bath, so as gradually to concentrate the acid.

7. Aconitine yields with phosphomolybdic acid (Sonnenschein's reagent) a yellow precipitate, which, in the presence of impurities, dissolves in ammonia with blue colour.

When the tongue-test renders the presence of an aconite base probable, it is very desirable to make a further physiological experiment on a small animal. For this purpose a quantity of residue or solution at least as great as that used for the tongue-test, and preferably several times as large, is made into one or more small pills with oatmeal, and given to a mouse or small bird by the mouth. It is distinctly preferable to operate in this manner rather than by hypodermic injection, in the case of such small

medical assistance could be obtained. On analysis, an alkaloidal substance was isolated from the stomach, which gave exactly similar colour-reactions to the alkaloid extracted by the same means from the *B.P.* tincture of aconite. It produced a distinct tingling sensation on the tongue and lips, and characteristic symptoms in a mouse which had eaten a portion of the extract made into a pill with oatmeal.

and sensitive animals as those which must almost necessarily be employed. If two healthy (white) mice be chosen, and one fed with ordinary oatmeal made into pills, and the other with oatmeal pills made with the alkaloidal extract, the symptoms may be readily compared, and several objections obviated. According to Wynter Blyth, a quantity of aconite extract sufficient to cause distinct numbness of the lips will kill a mouse or small bird if administered in this manner.[1] J. H. Munro (*Chem. News*, xlv. 110) has described an experiment in which he poisoned a sparrow with 0·1 grain of aconite root. Death ensued within an hour. The contents of the gizzard were mixed with the little which remained in the crop, and the alkaloid isolated. The extract did not respond to the taste or any chemical test; but the solution, when soaked up in bread-crumbs, and given to a tom-tit, killed the bird in two or three hours.

ATROPINE AND ITS ALLIES. TROPEÏNES.[2]

A remarkable series of natural alkaloids exist in the plants of the family *Solanaceæ*, and have been named, according to the plants in which they have been found, hyoscyamine and hyoscine, from *Hyoscyamus niger* (henbane) and *H. albus*; atropine and belladonnine, from *Atropa belladonna* (deadly nightshade); daturine, from *Datura stramonium* (thorn-apple); duboisine, from *Duboisia myoporoïdes*; scopolamine, from *Scopolia japonica*; mandragorine,[3] from *Mandragora vernalis*, &c. All these

[1] T. Stevenson found $\frac{1}{3000}$ grain of Morson's crystallised aconitine, hypodermically injected, fatal to a mouse in eighteen minutes. T. G. Wormley found Duquesnel's aconitine equally potent, $\frac{1}{3000}$ grain proving fatal to a mouse, after violent retching and convulsions, in thirty-two minutes.

[2] The author is indebted to Mr A. W. Gerrard and Mr R. Wright for perusal and correction of this section.

[3] Mandragorine, the alkaloid of the root of *Mandragora vernalis*, has been investigated by F. B. Ahrens (*Annalen*, ccli. 312; *Ber.*, xxii. 2159; *Jour. Soc. Chem. Ind.*, viii. 814, 915). The analysis best accords with the formula $C_{17}H_{27}NO_3$, but does not exclude the possibility of $C_{17}H_{23}NO_3$ representing the true composition. As extracted by ammonia and ether-chloroform, the base is obtained as a very deliquescent, colourless, vitreous mass, melting at 77°–79°. The *sulphate* forms small, white deliquescent plates, and the *hydrochloride* deliquescent needles. The *aurochloride* forms golden-yellow plates or needles melting at 153°–155°. BH_2PtCl_6 crystallises from hot water in yellow tables, melting with decomposition at 193°–194°. The *mercuro-chloride* crystallises from water or alcohol in slightly soluble needles or tables, which melt at 160°–161°. Mandragorine is precipitated by

bases are distinguished by a remarkable power of dilating the pupil, and hence are often termed the "mydriatic alkaloids," though the effect of pupil-dilation, or *mydriasis*, is not confined to the alkaloids of the *Solanaceæ*.

More recent investigations have reduced the number of the bases supposed to exist in the *Solanaceæ*. Thus, it appears that the bases isolated from *A. belladonna* and *D. stramonium* were simply a mixture of atropine and hyoscyamine in varying proportions, and that hyoscyamine is converted into atropine with such facility in presence of a trace of alkali, that it is not improbable that atropine does not always pre-exist in belladonna (see page 250). Similarly, the alkaloid described as duboisine is apparently identical with hyoscyamine, or with a mixture of that base and hyoscine.

Constitution of Atropine and its Allies.

The three best-known of the natural tropeïnes, viz., atropine, hyoscyamine and hyoscine, are all isomeric, being expressed by the formula $C_{17}H_{23}NO_3$. The associated bases belladonnine and atropamine differ from these by the elements of water, and are probably anhydro-bases (page 251). All these alkaloids are readily saponifiable, and traces of the products of their hydrolysis are therefore liable to pre-exist with them in the plant, or to be produced during the process of isolation. The following table exhibits the leading properties of the natural tropeïnes:[1]—

Base.	Formula.	Melting-Point, °C.	Specific Rotation.	Form.	Products of Saponificatio by Baryta.	
					Acid.	Base.
Atropine, .	$C_{17}H_{23}NO_3$	114·5	+0° to −1°·9	Needles.	Tropic acid.	Tropine.
Hyoscyamine,	$C_{17}H_{23}NO_3$	108·5	−21°	Needles or prisms.	Tropic acid.	Tropine.
Hyoscine, .	$C_{17}H_{23}NO_3$	...	...	Colourless syrup.	Tropic acid.	Pseudotro
Belladonnine,	$C_{17}H_{21}NO_2$	...	...	Amorphous.	Isomers of tropic and atropic acids.	Pseudotro
Atropamine, .	$C_{17}H_{21}NO_2$	Below 60	+0°	Varnish.		Pseudotro
Scopolamine, .	$C_{17}H_{21}NO_4$	...	...	...	Atropic acid.	Base me at 110°.
Benzoyl-pseudo-tropine,	$C_{17}H_{19}NO_2$	49	Inactive.	Radiating crystals.	Benzoic acid.	Pseudotro

picric acid, phosphotungstic acid, and iodised potassium iodide, which las yields an oily periodide. Mandragorine and its salts produce mydriasi whether introduced into the system or directly applied to the eye.

[1] The pre-existence of atropamine and belladonnine in the plants is nc absolutely established.

The natural tropeïnes are all easily saponified by treatment with acids or alkalies. By the latter (especially baryta) the hydrolysis results in the formation of tropic acid, or an isomer thereof,[1] and tropine or pseudotropine, in accordance with the equation :—

$$\underset{\text{Tropeïne.}}{C_{17}H_{23}NO_3} + H_2O = \underset{\text{Acid.}}{C_9H_{10}O_3} + \underset{\text{Base.}}{C_8H_{15}NO}.$$

When the hydrolysis is effected by an acid, especially concentrated hydrochloric acid, the tropic acid loses the elements of water, and atropic acid, $C_9H_8O_2$, results, and at a high temperature this is more or less changed into its polymers α- and β-isatropic acid, $C_{18}H_{16}O_2$. Such products also result from the saponification of the anhydro-bases belladonnine and atropamine by baryta.

The preferable method of effecting the saponification of the tropeïnes is to heat the alkaloid with saturated baryta-water to 60° or 80° C. for a few hours. Carbon dioxide is next passed through the liquid till a drop ceases to give a pink coloration with phenolphthaleïn. The liquid is then filtered, and the filtrate acidulated with hydrochloric acid and twice shaken with ether. The ether is separated, and on evaporation yields the acid product of the hydrolysis; on treating the aqueous layer with caustic alkali in excess and agitating with ether the basic product is extracted, and may be recovered by separating and evaporating the ether.

Tropic Acid, $C_6H_5.CH(CH_2.OH)CO.OH$, has the constitution of α-phenyl-β-hydroxypropionic acid. It crystallises from hot water in needles or slender prisms, and on the spontaneous evaporation of its aqueous solution in tablets which melt at 117°–118° C. Tropic acid is not volatile without decomposition. It has a slightly sour taste, dissolves in 40 parts of cold water, and is soluble in alcohol and ether. When heated with a dilute solution of potassium permanganate, tropic acid gives an odour of bitter-almond oil, and on further treatment, benzoic acid is produced.

Tropic acid has been prepared synthetically (*Ber.*, xiii. 2041).

Atropic Acid, $C_6H_5.C(CH_2).CO.OH$, has the constitution of α-phenylacrylic acid. It is isomeric with cinnamic acid (Part I. page 30), from which it differs by its solubility in water

[1] Except in the case of benzoyl-pseudotropine, which yields benzoic acid on hydrolysis.

(1 in 692 at 19°), its lower melting-point, and in not being precipitated by manganous salts from its neutral solutions. Atropic acid has been prepared synthetically, and may also be obtained by heating tropic acid with hydrochloric acid, or by the direct action of fuming hydrochloric acid at 120°, or boiling concentrated baryta-water, on atropine. It crystallises from hot water in needles, and from alcohol in tablets or monoclinic prisms, which melt at 106°–107°, are volatile with steam, and boil with decomposition at about 267°. Atropic acid is very soluble in carbon disulphide. It is oxidised to benzoic acid by chromic acid mixture, and yields formic and phenylacetic acids when fused with caustic potash. Sodium-amalgam reduces it to α-phenylpropionic acid. Bromine-water converts it into bromophenylpropionic acid.

Isatropic Acid, $C_{18}H_{16}O_4$, is polymeric with atropic acid, $C_9H_8O_2$, and is always formed together with that acid and tropic acid when atropine is heated with hydrochloric acid. Isatropic acid is always formed in small quantity when atropic acid is recrystallised from hot water, and more largely if the solution be boiled for some time.

Several isomeric modifications of isatropic acid exist; the *α-isatropic acid* is almost exclusively formed when atropic acid is heated for many hours to 140°–160° in a closed flask. It forms small warty crystals which melt at 237°, are very slightly soluble in water, and nearly insoluble in ether. It is not affected by sodium-amalgam or cold bromine-water. *β-isatropic acid* is formed together with much of the α-modification when the aqueous solution of atropic acid is boiled, and crystallises on cooling in small quadratic tablets, which melt at 206°, and are converted at 220°–225° into the α-acid. γ- and δ-isatropic acids were obtained by Liebermann by the saponification of truxilline (cocamine), a base contained in some varieties of coca leaves. From their source he subsequently named them α- and β-truxillic acids (compare page 286).

Tropine, $C_5H_7(C_2H_4.OH)N.CH_3$, has the constitution of a tetrahydropyridine, C_5H_9N, in which two of the hydrogen atoms are replaced respectively by methyl and hydroxyethyl. It is the basic product of the saponification of both atropine and hyoscyamine (see page 244). Tropine crystallises from absolute ether in rhombic tablets, melting at 61°–62° and boiling at 229°. It is hygroscopic, and very easily soluble in water and alcohol, remaining as an oil on evaporating these solutions. Tropine is a strong tertiary base and forms salts which crystallise well. $B_2H_2PtCl_6$ forms large, orange-red monoclinic prisms, easily soluble

in warm water, insoluble in alcohol, and melting with decomposition at 198°–200°. $BHAuCl_4$ forms large yellow plates, melting with decomposition at 210°–212°. The *picrate* is a yellow precipitate, crystallising from hot water in yellow needles. On ignition with soda-lime or caustic baryta, tropine yields methylamine, water and tropilidene:—$C_8H_{15}NO = CH_3NH_2 + H_2O + C_7H_8$. When heated with fuming hydrochloric acid to 180°, or with glacial acetic and strong sulphuric acid, it loses the elements of water and is converted into tropidine, $C_5H_6(C_2H_4)N.CH_3$, a liquid base boiling at 162°, smelling like conine, and interesting from its relation to anhydro-ecgonine (compare page 270).

Pseudotropine, $C_8H_{15}NO$, is isomeric with tropine, and results from the hydrolysis of hyoscine, belladonnine and atropamine. It forms rhombohedral crystals, melting at 106° and boiling at 241° to 243°. It is less hygroscopic than tropine, but very soluble in water and chloroform, and somewhat sparingly in ether. $B_2H_2PtCl_6$ forms small orange-red rhombic prisms, easily soluble in water. $BHAuCl_4$ forms small crystals melting at 198°.[1]

By treating pseudotropine with strong hydrochloric or sulphuric acid, a base isomeric with tropidine has been obtained.

Atropine. Daturine. Tropyl-tropine.

$C_{17}H_{23}NO_3$; or $C_5H_7(C_2H_4O.CO.CHC_6H_5.CH_2.OH)N.CH_3$.

Atropine is the characteristic alkaloid of *Atropa belladonna* or deadly nightshade, though it appears sometimes to be wholly or in great part replaced by its isomer hyoscyamine.[2] It

[1] The melting-point of the aurochloride is almost the only marked distinction between the pseudotropine produced by the hydrolysis of hyoscine and the (possibly identical) pseudotropine described by Liebermann (*Ber.*, xxiv. 2336), as resulting from the saponification of the *benzoyl-pseudotropine* discovered by Giesel in coca leaves from Java. After boiling this base with hydrochloric acid for some hours the benzoic acid formed was extracted with ether, and the acid liquid evaporated to dryness. The hydrochloride was decomposed by oxide of silver; or excess of strong caustic soda solution added, and the base extracted with ether. Pseudotropine thus obtained has a strong alkaline reaction, crystallises in beautiful needles, melts at 106°–107°, boils at 240°–241°, and is easily soluble in water, alcohol, and benzene; and is precipitated by petroleum spirit from the last solution. BHCl forms hygroscopic needles, the solution of which is precipitated white by mercuric chloride. BH_2PtCl_6 does not crystallise till the solution is evaporated nearly to dryness, but is then difficult to redissolve in water, and is precipitated on adding alcohol. $BHAuCl_4$ forms beautiful yellow needles, melting at 225°, and easily soluble in hot water and alcohol. The *picrate* forms easily soluble, yellow needles.

[2] See an interesting paper by Schütte, *Pharm. Jour.*, [3], xxii. 429 (from *Archiv*, October 30th, 1891, page 492).

also occurs in the seeds of *Datura stramonium* or thorn-apple, whence its name daturine.[1] Atropine has been prepared synthetically by heating together at 100°, with dilute hydrochloric acid, the tropic acid and tropine resulting from the hydrolysis of hyoscyamine (page 244). The direct conversion of hyoscyamine into atropine has also been effected (page 250), though the reverse change does not appear to have been realised.

Pure atropine forms tufts or groups of colourless or white lustrous needles, or acicular prisms. In commerce it often occurs as a crystalline or nearly amorphous yellowish powder. By prolonged exposure to air it gradually acquires a yellowish or darker tint. It melts when pure at 114° C. according to Ladenburg, or at 115°–115°·5 according to Schmidt; but the commercial alkaloid often begins to melt at about 104°, and is entirely melted at 113°.[2] At a higher temperature atropine shows signs of volatility, and, according to Dragendorff, volatilises slightly with steam, and even with alcohol-vapour. When dry, however, atropine does not lose weight by exposure to 100° C.

Atropine is odourless, but has a disagreeable bitter and acrid taste. It is a powerful poison, producing delirium and convulsions (page 261). From 0·05 to 0·2 gramme is commonly fatal, and 0·001 gramme the maximum medical dose for an adult. Much smaller amounts than this produce marked mydriasis or dilation of the pupil when applied to the eye (page 255).

Atropine is soluble in 600 parts of cold or 35 of boiling water; or, according to other authority, in 200 parts of cold and 54 of

[1] For the preparation of atropine from belladonna, the dried leaves should be macerated for several days in cold water, the liquid concentrated by evaporation, treated with sodium carbonate, and agitated with benzene. The benzene solution is separated and agitated with dilute sulphuric acid, and the acid liquid again rendered alkaline with sodium carbonate, and the liberated alkaloid extracted with chloroform, the solution in which, when mixed with petroleum spirit and allowed to evaporate spontaneously, deposits the atropine first, while the associated alkaloids remain in the mother-liquid. It is, perhaps, more easy to prepare atropine from belladonna *root*. Chloroform is the best solvent for the extraction of atropine from an alkaline liquid, but ether is preferable for its subsequent purification and crystallisation (A. W. Gerrard).

[2] In a private communication to the author, A. W. Gerrard states that pure atropine melts at 114°–115°. If some of the same sample be placed in water it melts at 83°–84°. This result is evidently due to hydration, for the substance, after contact with water, melts at the same temperature in a capillary tube; but by exposure over strong sulphuric acid the alkaloid loses its water, and then again melts at 114°–115°. Operating on the same specimen of atropine as Gerrard, the author observed a melting-point of 114°·5, when a fragment of the substance was heated on the surface of mercury contained in a test-tube immersed in a bath of paraffin.

boiling water. The aqueous solution undergoes rapid change in contact with air, becoming yellow and acquiring a disagreeable smell, but without losing its toxic character. Atropine dissolves in glycerin, and is readily soluble in alcohol, ether (60 parts), chloroform (3 parts), amylic alcohol and benzene (42 parts), but is only slightly soluble in petroleum spirit or carbon disulphide. The solutions are optically inactive, or very feebly lævo-rotatory.

The aqueous solution of atropine exhibits a distinct alkaline reaction to litmus, and also reddens phenolphthaleïn, the latter character distinguishing atropine and its isomers from almost all other known alkaloids (page 256).

Other reactions of atropine are described on page 254, *et seq.* By treatment with alkalies or mineral acids, atropine readily undergoes saponification (page 245), but is not altered by boiling with strong tartaric acid (compare page 206). By strong nitric acid it is converted into anhydro-atropine (page 251).

Atropine Sulphate, $B_2H_2SO_4$, prepared by neutralising atropine with dilute sulphuric acid and evaporating the solution to dryness at 100°, is colourless and odourless, neutral, easily soluble in water and alcohol, but less readily in ether. The commercial salt is usually faintly alkaline, and keeps better when so made. The aqueous solution should be neutral or faintly alkaline to litmus.

According to E. Schmidt, the more hyoscyamine a sample of commercial atropine sulphate contains the finer is its crystalline appearance, the pure salt occurring as granular white masses. The absence of hyoscyamine is shown by the solution of the sample being optically inactive.

Atropine borate and *valerate* are employed in ophthalmic surgery.

Commercial Atropine and its Salts should be free from yellow colour, and should not become coloured on treatment with strong sulphuric acid or excess of ammonia. The substance should leave no appreciable residue on gentle ignition. A drop of a solution in 1000 parts of water should have an acrid and bitter taste, and yield a non-lustrous golden-yellow precipitate with a drop of auric chloride, which melts under boiling water. One drop of a solution of atropine in 45,000 parts of water (or less than 2 grains per gallon), when placed in the human eye, should cause dilation of the pupil in from forty to sixty minutes.

Hyoscyamine. Daturine. Duboisine. $C_{17}H_{23}NO_3$.

This base occurs in belladonna, stramonium, and other solanaceous plants in association with atropine,[1] with which alkaloid it

[1] Hyoscyamine occurs in the seeds, leaves, and roots of henbane and other species of *Hyoscyamus*, in association with hyoscine. It accompanies atropine

is isomeric; indeed Ladenburg (*Ber.*, xxi. 3065) holds that atropine is an optically inactive base, standing to the active hyoscyamine in the same relation as racemic acid stands to lævo-tartaric acid. At any rate, by keeping hyoscyamine at a temperature slightly above its melting-point the optical activity gradually falls, and the product is found to consist of atropine.[1] Conversion of hyoscyamine into atropine also occurs when its cold alcoholic solution is allowed to stand after a slight addition of caustic potash or soda, or even of ammonia; but as the specific rotation of the product never falls below $-1°{\cdot}9$, whereas pure atropine is wholly inactive, it appears probable that the transformation is incomplete.[2]

Hyoscyamine forms slender colourless needles, which sometimes radiate in groups. In its solubilities and general chemical characters it presents a close resemblance to atropine, which it also simulates in its physiological effects. The distinctions between the bases are given on page 254.

Hyoscyamine Sulphate, $B_2H_2SO_4$, forms small golden-yellow or yellowish white crystalline scales, or a yellowish white amorphous powder, melting at 260° and deliquescing on exposure to air.

Hyoscine. $C_{17}H_{23}NO_3$.

(See also page 244.) Hyoscine occurs, together with hyoscyamine, in the leaves and seeds of *Hyoscyamus niger* (henbane). The "amorphous hyoscyamine" of commerce appears in many cases to consist chiefly of hyoscine. Hyoscine should be carefully differentiated from atropine and hyoscyamine, as its mydriatic effects appear to be more rapid and powerful than those produced by the latter bases; and, taken internally in doses of $\frac{1}{85}$ grain, it produces effects distinct from those of atropine.[3]

Free hyoscine forms a thick syrup, having a close general

in *Atropa belladonna* (deadly nightshade), in which it is sometimes present to the exclusion of atropine, which, according to Will, is not unfrequently formed from the hyoscyamine during the process of isolation. Hyoscyamine also occurs in association with atropine in the seeds of *Datura stramonium* (thorn-apple); with hyoscine in the root of *Scopolia japonica* and *S. atropoïdes;* and almost alone in the root of *S. carniolica* and the leaves and twigs of *Duboisia myoporoïdes*. According as commercial hyoscyamine has been prepared from one or other of the above sources, it is liable to contain more or less of the associated alkaloids.

[1] E. Schmidt (*Pharm. Zeit.*, 1889, page 583) has obtained some indication of the formation of another alkaloid besides atropine in this reaction.

[2] Schütte has recently found (*Pharm. Jour.*, [3], xxii. 429), that conversion into atropine occurs when hyoscyamine is kept long in solution or in the form of aurochloride, or is repeatedly crystallised from acidulated water.

[3] The calmative and sedative effects of henbane, which distinguish it in physiological action from belladonna and stramonium, are undoubtedly due to the predominating alkaloid, hyoscine.

resemblance to hyoscyamine and atropine, but yielding pseudo-tropine instead of tropine on saponification (page 247). The reverse reaction has not been realised.

Other characters of hyoscine, and distinctions from hyoscyamine and atropine, are given on page 254.

Hyoscine Hydrobromide should occur in colourless rhombic crystals, losing 12·3 per cent. of their weight when dried at 100°. With Vitali's test (page 257) it should give a violet coloration. Commercial hyoscine hydrobromide is liable to contain a large proportion of the corresponding salt of scopolamine, and, according to E. Schmidt, often essentially consists of this salt.[1]

BHI forms pale golden prisms, the solution of which is lævo-rotatory. $BHAuCl_4$ crystallises in prisms, melts at 200°, and is sparingly soluble in water.

Anhydro-Tropeïnes.

Apo-atropine, $C_{17}H_{21}NO_3$, preferably called *anhydro-atropine*, differs from atropine by the elements of water, and hence is isomeric with atropamine and belladonnine. It is obtained by gradually adding atropine to fuming nitric acid maintained at about 50° C. On rendering the liquid alkaline and extracting with ether, the new base is dissolved, and is obtained on evaporating the solvent as an oil, or prisms melting at 60°–62°, slightly soluble in water, but readily in chloroform. Apoatropine is not mydriatic or irritating to the eye, and apparently not poisonous. It yields a crystalline *sulphate*, sparingly soluble in cold water. The *chloroplatinate* is crystalline, and, unlike that of atropine, only sparingly soluble in hydrochloric acid. The *aurochloride* is amorphous, and melts at 180°. Anhydroatropine is hydrolysed by boiling baryta-water, forming tropine and atropic acid.

Atropamine, $C_{17}H_{21}NO_2$ (page 244), is not a constant constituent of belladonna, and, owing to the readiness with which it undergoes change, it is liable to escape recognition. It was

[1] Scopolamine, or Scopoleïne, $C_{17}H_{21}NO_4$, was first found in the root of *S. atropoïdes*, and has since been isolated in small quantities from belladonna root, stramonium seeds, and *D. myoporoïdes*. In one case the mydriatic alkaloid of the last-named plant consisted essentially of scopolamine, while the base from another sample of the leaves was essentially hyoscyamine. Scopolamine appears to contain a hydroxyl-group, as it forms an acetyl-derivative, while towards nitrous acid it behaves as a tertiary base. By boiling with baryta it is hydrolysed with formation of atropic acid and a crystalline base melting at 110° C. *Scopolamine hydrobromide* forms large glassy crystals. The *aurochloride* forms long shining needles, presenting a peculiar comb-like or serrated appearance at the margin. When anhydrous, the aurochloride melts at 214°, and is nearly insoluble in water.

isolated by Hesse (*Annalen*, cclxi. 87) by dissolving in acetic acid the alkaloids left in the mother-liquor after the preparation of atropine, and adding common salt to the solution until a milky turbidity was produced. On standing, the hydrochloride crystallises out, and can be obtained pure by recrystallisation from boiling water after treatment with animal charcoal. On treating the hydrochloride with dilute ammonia and ether, the atropamine dissolves, and may be obtained as a soft colourless varnish on evaporation. At 60° it forms a colourless, odourless liquid, which does not lose weight at 100°. It is only sparingly soluble in water and petroleum ether, but very readily in alcohol, ether, chloroform and benzene. The alcoholic solution is optically inactive, has a bitter taste, does not redden phenolphthaleïn (distinctive from atropine), but colours red litmus-paper blue and neutralises acids. Atropamine possesses no mydriatic properties, but produces a burning sensation and inflammation when dropped into the eye, whereas apo-atropine is inactive.

Atropamine is considered by Hesse to bear the same relation to hyoscine that anhydro-atropine bears to its parent-base, and is isomeric with belladonnine, from which it differs in ready crystallisability of its hydrochloride and hydrobromide, a fact which affords a ready means of separating it from the other alkaloids of belladonna. If the hydrochloride or hydrobromide of atropamine be moistened with a mineral acid, and warmed or exposed to sunlight, the base is readily converted into belladonnine.

Atropamine is also transformed into belladonnine by solution in cold concentrated sulphuric acid, or by the mere evaporation of the solution of its sulphate. Dilute sulphuric acid also effects the conversion, but a preferable plan is to heat atropamine with moderately concentrated hydrochloric acid to about 80°. If the solution be boiled, or if baryta-water be employed as the converting agent, the belladonnine first formed undergoes hydrolysis, so that atropamine and belladonnine ultimately yield the same saponification products.

BELLADONNINE, $C_{17}H_{21}NO_2$ (page 244), is isomeric with anhydro-atropine and atropamine.[1] Its formation from the latter substance is described above. Belladonnine forms a varnish-like mass, very sparingly soluble in water, but readily in alcohol, ether, chloroform and benzene. The salts are amorphous. $B_2H_2PtCl_6$ and $BHAuCl_4$ are yellow pulverulent precipitates, quite insoluble in cold water. Crude belladonnine is said to contain *oxytropine*, $C_8H_{15}NO_2$, a crystallisable base melting at 242°.

When belladonnine is boiled with baryta-water, or moderately

[1] According to Ladenburg the formula of belladonnine is $C_{17}H_{23}NO_4$, and it is converted by hydrolysis into tropic acid and oxytropine.

concentrated hydrochloric acid, it is hydrolysed with formation of pseudotropine, $C_8H_{15}NO$, and two acids of the formula $C_9H_{10}O_3$ and $C_9H_8O_2$; but as both these bodies are amorphous they appear to be isomeric, and not identical with tropic and atropic acids respectively. When atropamine or belladonnine is heated at 100° with fuming hydrochloric acid, pseudotropine and crystallisable atropic acid are formed, instead of the foregoing amorphous acids.

Artificial Tropeïnes.

When tropine (page 246) is treated with benzoyl chloride it yields benzoyl-tropine, $C_5H_7(C_2H_4.OBz)N.CH_3$, which is the type of a series of bodies called *tropeïnes* (Ladenburg), having the constitution of esters of tropine. The natural mydriatic alkaloids belong to this class, and atropine has actually been obtained synthetically by heating tropine with tropic acid.

Benzoyl-tropine, $C_5H_7(C_2H_4.OC_7H_5O)NCH_3$, is a crystallisable substance which forms salts very similar to those of atropine. It is a powerful local anæsthetic, and when applied to the eyes produces the dilation characteristic of the natural tropeïnes. *Benzoyl-pseudotropine* occurs naturally in certain coca leaves from Java (page 287).

Salicyl-tropine, $C_5H_7(C_2H_4.O.C_7H_5O_2)NCH_3$, is obtained by evaporating to dryness a mixture of salicylic acid and atropine with dilute hydrochloric acid. It is a weak poison, devoid of action on the pupil.

Homatropine, $C_{16}H_{21}NO_3$, is an artificial base having the constitution of a lower homologue of atropine. It is prepared by evaporating a mixture of tropine (from the saponification of hyoscyamine) and mandelic acid, with dilute hydrochloric acid. Mandelic acid itself is produced by the action of hydrochloric acid on amygdalin, the glucoside of almonds. It is the lower homologue of tropic acid, and has the constitution of a phenyl-glycollic acid:—

$$C_6H_5.CH\begin{cases}CO.OH\\OH\end{cases} \qquad C_6H_5.CH\begin{cases}CO.OH\\CH_2.OH\end{cases}$$

Mandelic acid. Tropic acid.

Homatropine crystallises from absolute ether in prisms which melt at 98° C. It is very deliquescent, and hence is usually obtained as a syrup. It dissolves sparingly in water, but freely in ether and chloroform.

Homatropine behaves like atropine with Gerrard's test, but with Vitali's test (page 257) it yields a yellow instead of a violet coloration. With Mayer's reagent the salts yield a white, curdy

precipitate, and with picric acid a yellow precipitate soon becoming crystalline.

Homatropine resembles atropine in its general physiological effects, but is less toxic, and in small doses is a true hypnotic. It dilates the pupil as powerfully as atropine, but the effect subsides far more rapidly, and hence the base has proved valuable in ophthalmic surgery.

Homatropine Sulphate crystallises in silky needles. The *hydrochloride* is crystallisable and very soluble. The *chloroplatinate* is deposited from concentrated solutions in fine crystals. $BHAuCl_4$ is described on next page.

Homatropine Hydrobromide, $C_{16}H_{21}NO_3$, HBr, crystallises in non-deliquescent, flat rhombic prisms or plates which form wart-like aggregations. According to the *British Pharmacopœia* (Additions, 1890) it is a white crystalline powder or aggregation of minute prismatic crystals, soluble in 6 parts of cold water and 133 of alcohol.[1]

Detection and Determination of Tropeïnes.

Atropine and the allied bases present a close general resemblance, alike in their physical, physiological, and chemical characters. The following table shows the principal distinctions between them :—

	Atropine.	Hyoscyamine.	Hyoscine.
Appearance,	Needles or acicular prisms.	Slender, radiating needles or crystalline powder.	Syrup.
Melting-point, °C.	114·5	108·5	...
Optical activity,	Inactive or feebly lævo-rotatory.	$S_D = -21°$, in alcoholic solution.	...
Reaction of free base with alcoholic mercuric chloride (page 256),	Red precipitate.	Yellow or red precipitate.	White precipitate.
Characters of mercurochloride,	Gummy precipitate.	Oil, solidifying to plates.	Amorphous or oily.
Characters of platinochloride,	Not ppted. from 5 per cent. solutions. On evaporation, forms monoclinic crystals, melting at 207°.	Not ppted. from 5 per cent. solutions. On evaporation, forms beautiful triclinic crystals, melting at 200°.	Small octohedra; soluble in water, alcohol and ether-alcohol.
Characters of aurochloride,	Lustreless; yellow, melts at 135°-138°.	Lustrous, golden-yellow scales, melting at 160°-162°.	Yellow prisms, melting at 198°-200°.
Basic product of saponification,	Tropine, melting at 61°-62°.	Tropine, melting at 61°-62°.	Pseudotropine, melting at 106°.

[1] "If 2 minims of chloroform be shaken with 10 minims of a 10 per cent. aqueous solution, and chlorine-water be cautiously added, the chloroform will assume a brownish colour. A 2 per cent. aqueous solution is not precipitated

The reactions of the tropeïnes with auric chloride form the best distinctions between them. *Atropine aurochloride* is thrown down from dilute solutions as an amorphous or oily precipitate which gradually becomes crystalline. Under the microscope it appears in rosettes and other very characteristic forms. It melts under hot water, and is deposited from its solution in boiling water acidulated with hydrochloric acid in minute crystals, which are *lustreless* after drying, and melt at 135°–138°. *Hyoscyamine aurochloride* is precipitated in brilliant, irregular, golden-yellow scales, appearing under the microscope in quadratic forms. It retains its lustre when dry, and melts at 160°–162°. *Hyoscine aurochloride* crystallises in yellow prisms which melt at 198°–200°, and are less soluble and less lustrous than the hyoscyamine salt. *Homatropine aurochloride* is at first oily, but soon crystallises in prismatic forms. *Scopolamine* aurochloride is described on page 251.

Ladenburg employs the aurochlorides to separate the tropeïnes from each other. The atropine salt is the most insoluble and in fractional precipitation is thrown down first, while the hyoscyamine salt is the most readily soluble. The alkaloids may be recovered by decomposing the aurochlorides with sulphuretted hydrogen, adding ammonia to the filtrate, and agitating with chloroform or ether.

The foregoing properties and reactions are almost the only ones affording fairly sharp distinctions between atropine and its isomers. The following reactions are (when not otherwise stated) common to the three bases, and distinguish them from other alkaloids.

a. By far the most delicate test for the tropeïnes is their power of producing *mydriasis* or dilation of the pupil of the eye. Dilation from the application of a solution weaker than 1 in 500 causes little inconvenience to the human eye, but solutions far weaker produce the effect quite distinctly, and even powerfully, and the eye of a young cat, dog, or rabbit is to be preferred. In making such an experiment, an aqueous solution must be prepared either of the free alkaloid or its sulphate or acetate. The solutions

by the cautious addition of a solution of ammonia previously diluted with twice its volume of water. About a tenth of a grain moistened with 2 minims of nitric acid, and evaporated to dryness on the water-bath, yields a residue which is coloured yellow by an alcoholic solution of potash. If about a tenth of a grain be dissolved in a little water, and the solution be made alkaline with ammonia and shaken with chloroform, the separated chloroform will leave on evaporation a residue which will turn yellow, and finally brick-red, when warmed with about 15 minims of a solution of 2 grains of perchloride of mercury in 100 minims of proof spirit."—*British Pharmacopœia* (Additions, 1890).

should be neutral or only feebly alkaline, not strongly contaminated even with neutral salts, and not alcoholic. A drop or two of such a solution is placed by means of a pipette or glass rod on one of the eyes, and the size of the pupil compared with that of the fellow-eye from time to time. E. R. Squibb (*Ephemeris*, ii. 855) states that distinct mydriasis is produced by a solution of 0·000000427 gramme of atropine sulphate in less than an hour. Such an intense effect is quite peculiar to atropine and its isomers (hyoscine is even more powerfully mydriatic), but more or less dilation of the pupil is also produced by cocaine and preparations of hemlock (conine) and digitalis. Aconitine has a variable effect, and nicotine is said first to dilate and then to contract the pupil. Certain ptomaines exert a mydriatic effect.

b. Free atropine, as obtained by evaporating its chloroformic or ethereal solution (after liberation of the alkaloid from one of its salts by ammonia), gives a red colour with phenolphthaleïn. This reaction is common to hyoscyamine and hyoscine, and is also produced by the artificial base homatropine, but is not given by any other alkaloid in common use (except, according to Plugge, the volatile bases conine and nicotine). Flückiger, who first observed the peculiar behaviour of the tropeïnes with phenolphthaleïn (*Pharm. Jour.*, [3], xvi. 601), recommends that a minute quantity of the alkaloid to be tested should be placed on phenolphthaleïn paper, which is then wetted with strong alcohol. No coloration will be produced at first, but on allowing the alcohol to evaporate, and touching the alkaloid with a drop of water, a brilliant red coloration will appear. On adding alcohol the colour is destroyed, but appears again as the spirit evaporates.[1]

c. When a solution of mercuric chloride in proof-spirit is cautiously added to free atropine (as obtained by evaporation of a chloroform solution after liberation of the alkaloid by ammonia), avoiding excess, a red precipitate is produced. A. W. Gerrard, who first described this reaction (*Pharm. Jour.*, [3], xiv. 718), states that the precipitate consists of mercuric oxide (with a trace of mercurous oxide), and expresses the reaction by the following equation:—$2C_{17}H_{23}NO_3 + HgCl_2 + H_2O = HgO + 2C_{17}H_{23}NO_3,HCl$. The atropine hydrochloride reacts with an additional quantity of mercuric chloride to form the double chloride $BHCl,2HgCl_2$, which separates in crystalline tufts when the liquid is allowed to stand for a few hours. In a more recent paper (*Pharm. Jour.*, [3], xxi. 898) Gerrard has modified and more precisely defined the method of making the test as follows:—0·1 grain of the free alkaloid

[1] This behaviour is peculiar. Caustic alkalies react perfectly with phenolphthaleïn in alcoholic solution.

(extracted from a salt by ammonia and chloroform) is placed on a watch-glass or in a test-tube, and 20 minims of a 2 per cent. solution of mercuric chloride in proof-spirit gradually added. A red coloration is yielded at once by *atropine*. *Hyoscyamine* at first becomes yellow, then darkens a little, and finally, on heating, a well-marked red precipitate is formed. If a large excess of hyoscyamine be used, merely a yellow precipitate is formed, while with a large excess of the reagent no precipitation occurs.[1] *Homatropine* (page 253) also yields a red precipitate under the conditions of the test; but *hyoscine* gives neither a red nor a yellow coloration or precipitate, and hence is sharply distinguished from the other tropeïnes. Gerrard found no red or yellow precipitate to be produced by strychnine, brucine, morphine, codeine, veratrine, aconitine, conine, gelsemine, caffeine, cinchonine, cinchonidine, quinine or quinidine; though most of these bodies gave white precipitates, which in the cases of codeine and morphine became pale yellow on heating. This behaviour has been confirmed by Schweissinger (*Arch. Pharm.*, [3], xxii. 827), who also states that cocaine gives a white precipitate (only appearing in strong solutions and soluble on warming) and scoparine a yellow precipitate with mercuric chloride; while strychnine, caffeine, arbutine, sparteine and condurangine are stated to yield no reaction. Schweissinger suggests that the test might be made quantitative for atropine by determining the mercuric oxide precipitated; but this would only be possible in the absence of alkaloids or other substances giving precipitates of any kind with mercuric chloride. The value of Gerrard's test has also been confirmed by Flückiger (*Pharm. Jour.*, [3], xvi. 601), who found cocaine to give a pure white precipitate which very soon turned red.

d. Gerrard has also observed (*Pharm. Jour.*, [3], xvi. 762) the liberation of mercurous oxide from calomel and other mercurous salts by the action of atropine. If atropine be dissolved in alcohol, and four measures of water added, the solution will immediately precipitate black mercurous oxide from a solution of mercurous nitrate free from excess of acid. This is best prepared by adding caustic soda, drop by drop, to a solution of mercurous nitrate until a slight permanent precipitate is produced, and then filtering.

e. D. Vitali has observed that if a minute quantity of solid atropine be treated with a drop of fuming nitric acid, the liquid

[1] Harnack (*Chem. Zeit.*, xi. 52) disputes the identity of hyoscyamine and duboisine, and states that the former gives a clear solution with Gerrard's reagent, a slight turbidity appearing on continued heating, while duboisine gives a white turbidity immediately, and on warming a white precipitate.

evaporated at 100°, and the residue when cool touched with a drop of a *freshly-prepared solution of caustic potash in absolute* alcohol, a magnificent violet coloration is produced, which slowly changes to dark red and ultimately disappears, but can be reproduced by adding more alcoholic potash. The violet reaction is almost peculiar to atropine and its isomers, and is said to be produced by 0·0001 milligramme of the alkaloid. Out of some sixty alkaloids examined no others were found to give a violet coloration. The coloration is not produced if aqueous potash be substituted for the alcoholic solution. Strychnine gives a red, brucine a greenish, and homatropine a yellow colour when similarly treated. Arnold (*Arch. Pharm.*, 1882, page 564) modifies the test by moistening the alkaloid with strong, cold sulphuric acid, and then adding a fragment of sodium nit*rite*. With atropine a yellow colour is produced, which, on applying alcoholic potash, changes to reddish violet and then to pale rose. Strychnine gives an orange-red colour, but homatropine behaves like atropine. Alkaloids which yield strong colorations before the application of the alcoholic potash (*e.g.*, morphine, narcotine, narceine) render the test inapplicable. Flückiger (*Pharm. Jour.*, [3], xvi. 601) recommends that 1 milligramme of atropine and about the same quantity of sodium nitrate should be rubbed together with a glass rod, the end of which has been moistened with a very little concentrated sulphuric acid. A saturated solution of caustic soda in absolute alcohol is then added drop by drop; when in presence of atropine a red or violet colour will be produced. When sodium nitrite is substituted for the nitrate in the above test, an orange mixture is obtained, which, on dilution with a strong aqueous solution of caustic soda, turns in succession to red, violet and lilac.

E. Beckmann (*Arch. Pharm.*, [3], xxiv. 481) has pointed out that veratrine behaves somewhat similarly to atropine with Vitali's test; but states that with nitrous acid or a nitrite instead of nitric acid, and aqueous instead of alcoholic potash, atropine gives a reddish violet coloration, and veratrine a yellow one.

f. When atropine is heated to the boiling-point with a mixture of equal measures of glacial acetic and strong sulphuric acids no coloration is produced; but after a time the liquid exhibits a well-marked yellowish or brownish green fluorescence. After cooling, the liquid has a pleasant aromatic odour in addition to that of acetic acid. The behaviour of other tropeïnes with this test, which is due to E. Beckmann, does not appear to have been recorded. Veratrine gives a similar brownish fluorescent liquid, but during the previous heating the solution acquires an intense cherry-red colour.

g. According to A. Wynter Blyth, if a particle of atropine be

treated with a few drops of concentrated baryta solution, the liquid evaporated to dryness, and the residue strongly heated, an agreeable odour resembling that of hawthorn-blossom will be perceived.

h. According to the *German Pharmacopœia,* if at least 0·001 gramme of atropine sulphate be heated in a small test-tube until white vapours appear, and 1·5 gramme (=0·8 c.c.) of sulphuric acid be then added, and the heating continued until the mixture begins to turn brown, on then adding 2 c.c. of water an agreeable odour will be perceived; and on further adding a crystal of potassium permanganate, the odour of bitter-almond oil will be obtained.

i. A saturated solution of bromine in hydrobromic acid[1] gives with atropine and its salts, even in very dilute solutions (1:10,000), a yellow amorphous precipitate, which in a short time becomes crystalline. The precipitate from somewhat strong solutions of the alkaloid disappears after a time, but is immediately reproduced on adding more of the reagent. The precipitate is insoluble in acetic acid, and only very sparingly soluble in a large excess of the mineral acids or fixed caustic alkalies. It is even produced from a solution of atropine in concentrated sulphuric acid. The microscopic appearance of the precipitate is highly characteristic, exhibiting under a magnifying power of 75 to 125 diameters lanceolate, leaf-like crystals, grouped together like the petals of a flower. These forms may be obtained by the spontaneous evaporation of a drop of liquid containing only $\frac{1}{25000}$ grain of atropine. If not produced, a drop of water should be added, and evaporation repeated. T. G. Wormley, who is the observer of the reaction, considers the formation of the crystals quite characteristic of atropine or hyoscyamine. Most alkaloids give yellow precipitates with Wormley's reagent, but all these deposits, except those produced by atropine, hyoscyamine and meconin, remain amorphous; and that produced by the last-named substance has quite a different microscopic appearance from those formed by the mydriatic alkaloids. The behaviour of hyoscine with Wormley's reagent has not been recorded.

**j.* A solution of iodine in iodide of potassium throws down, from solutions of atropine, hyoscyamine and hyoscine, acidulated with hydrochloric acid, the whole of the alkaloid as a reddish brown or dark green amorphous precipitate of the tri-iodide, insoluble in acetic acid, but somewhat affected by other acids. Dunstan and Ransom (*Pharm. Jour.*, [3], xiv. 625) recommend the reagent for

[1] Wormley states that in the absence of hydrobromic acid, a solution of bromine in alcohol may be used. A solution in hydrochloric acid would appear preferable.

the purification and determination of atropine and its isomers. For this purpose they dissolve the alkaloid in dilute hydrochloric acid, and add excess of a strong solution of iodine in potassium iodide. The precipitate at once agglomerates, and is filtered off, slightly washed with the solution of iodine, and then decomposed by pouring on the filter a solution of sodium thiosulphate, which dissolves it to a colourless liquid, from which the alkaloid is recovered by addition of ammonia and agitation with chloroform.

k. Mayer's reagent precipitates atropine and its isomers from solutions not too dilute, and has been employed with limited success for their quantitative determination. The characters of the precipitate and the best method of operating have already been fully described (page 140 *et seq.*).

l. Potassio-iodide of bismuth and potassio-iodide of cadmium precipitate atropine from highly dilute solutions. Their reactions with the isomeric alkaloids have not been recorded.

m. Phosphomolybdic and phosphotungstic acids precipitate atropine and its isomers from somewhat dilute solutions, and are of service for concentrating the alkaloids and separating them from other organic matter.

n. An alcoholic solution of picric acid yields a yellow amorphous precipitate in solutions of atropine which are not too dilute. The precipitate becomes crystalline after a time, and appears under the microscope in highly characteristic forms. With hyoscyamine, picric acid yields an oily precipitate, rapidly solidifying to right-angled laminæ, very similar to those formed by atropine picrate.

The reactions of atropine and its isomers with other reagents are not characteristic. Potassium iodide, thiocyanate, ferrocyanide, ferricyanide and chromate fail to precipitate even concentrated solutions of these alkaloids.

Atropine and its allies are not removed from acidulated solutions by agitation with immiscible solvents. From solutions rendered alkaline by ammonia, or an alkali-metal carbonate, they are readily and completely extracted by chloroform, and with less facility by ether. The separated solution may be evaporated, and the residue dried without loss at 100°. The bases thus isolated are distinguished from all other well-known alkaloids by their power of reddening phenolphthaleïn (test *b*), and (with the exception of hyoscine) giving a red precipitate when warmed with an alcoholic solution of mercuric chloride (test *c*). The alkaloidal residue may be titrated with standard hydrochloric acid, using litmus or methyl-orange as an indicator, and further purified, if desired, by converting the resultant hydrochlorides into the tri-iodides (test *e*), and recovering the alkaloids from the precipitates.

TOXICOLOGICAL DETECTION OF ATROPINE AND ITS ALLIES.

Atropine, hyoscyamine and hyoscine are all highly poisonous. Cases of poisoning by the pure alkaloids are rare, but both criminal and accidental poisoning by the plants of which they are the active principles have been frequent; and, in India, poisoning by stramonium has achieved the position of a profession.

The symptoms of poisoning by atropine and its isomers are thus described by A. Swaine Taylor:—Heat and dryness of the mouth and throat, nausea, vomiting, giddiness, indistinct or double vision, delirium, great excitement and restlessness, convulsions followed by drowsiness, stupor, and lethargy.[1] The pupils are much dilated and the eyes insensible to light. Occasionally the pupils are contracted during sleep, although dilated in the waking state. The symptoms often come on very soon after taking the poison, while recovery may be delayed for several days, or even weeks. The symptoms of poisoning by *stramonium* are very similar to those produced by belladonna and hyoscyamus, but more severe. Ringing in the ears, dryness of the throat, and flushed face are early symptoms. Delirium of a violent kind, with spectral illusions, comes on rapidly, and the pupils are widely dilated. There is often paralysis of the lower extremities.

The *post-mortem indications* of poisoning by atropine and its isomers are not characteristic, except that the pupils are dilated. The brain and its membranes are found congested. Where solid parts of a solanaceous plant have been eaten the fragments may often be found in the stomach, and identified by their botanical and microscopic characters.

The detection of atropine and its isomers in cases of poisoning may be effected by the Stas-Otto process. Heating with alkalies or mineral acids must be avoided, or the alkaloid may undergo hydrolysis (page 245). Hence tartaric or acetic acid should be used to acidify the matters to be examined. Ammonia or a carbonate of alkali-metal should be used to liberate the alkaloid, and ether or (preferably) chloroform employed for its extraction. The tests most serviceable for the recognition of atropine and its isomers in cases of poisoning are:—

1. The dilation of the pupil (page 255).
2. The reactions of the free alkaloid, as obtained in the chloroform-residue, with phenolphthaleïn and a spirituous solution of mercuric chloride.

[1] The symptoms of atropine poisoning, especially in children, are not unlike those of scarlet fever. Some cases resemble *rabies*, and the garrulous delirium and hallucinations of an adult are very similar to those of *delirium tremens*.

3. The reaction of a solution of the alkaloid with bromine (page 259), and the microscopic appearance of the precipitate.

4. The production of a violet colour by Vitali's test (page 257).

5. The evolution of an agreeable odour when the alkaloid is evaporated to dryness with baryta-water, and the residue heated.

6. The microscopic appearance of the picrate.

Atropine does not appear to suffer change in the body after death. It has been detected after a considerable interval of time. Ptomaines having a mydriatic action have been met with.

Belladonna, Henbane, and Stramonium.

Atropa belladonna or deadly nightshade,[1] *Hyoscyamus niger* or henbane,[2] and *Datura stramonium* or thorn-apple[3] are the three chief sources of the tropeïnes; but these or similar alkaloids are found in a number of allied species, and the poisonous alkaloid solanine occurs in all the species of *Solanum*, as well as in other members of the *Solanaceæ*.[4]

In addition to the alkaloids, which are probably in combination with malic acid, *belladonna root* contains cellulose, starch, sugar, inulin, asparagin, fatty matter, a fluorescent substance,[5] and

[1] French, *la Belladone, la Morelle furieuse;* German, *Tollkirsche, Wolfskirsche, Tollkraut.*

[2] French, *la Jusquiame;* German, *Bilsenkraut.*

[3] French, *Stramoine;* German, *Stechapfel.*

[4] A minute proportion of an alkaloid, apparently identical with hyoscyamine, has been found in lettuce by T. S. Dymond (*Proc. Chem. Soc.*, 1891, p. 165).

[5] The fluorescent substance contained in belladonna root, and present also in the leaves and stalk, is called by H. Kunz (*Arch. Pharm.*, [3], xxiii. 722) *chrysatropic acid*, and is said to have the formula $C_{12}H_{10}O_5$. H. Paschkis (*Arch. Pharm.*, [3], xxiii. 541; xxiv. 155) has isolated what is apparently the same body from the berries of ripe belladonna, and ascribes to it the formula $C_{10}H_8O_4$. He considers it identical with the scopoletin obtained by Eykman from *Scopolia japonica.* It forms pale yellow, rhombic prisms or needles, melting at 198°–201°, and subliming without decomposition when carefully heated. It dissolves in about 80 parts of hot water, more sparingly in cold water and ether, but readily in acetic acid, alcohol, chloroform, amylic alcohol and benzene. It is extracted by the last three solvents from its aqueous solution. The aqueous, alcoholic and ammoniacal solutions exhibit a splendid blue fluorescence when dilute, and emerald-green when concentrated. The fluorescence is destroyed by acids. Ferric chloride gives an emerald-green coloration changing to cobalt-blue. Fehling's solution and ammonio-nitrate of silver are reduced on warming. In moderately concentrated nitric acid the substance dissolves with yellow colour, changed to blood-red by ammonia. (This reaction resembles that of æsculin, observed by Sonnenschein.)

Kunz isolated chrysatropic acid by treating the extract of belladonna with acid and agitating with ether. On evaporating the ether, and washing the

a red colouring-matter called atrosin, which is also found in considerable quantity in the berries. The proportion of starch in young belladonna roots is considerable, but it is present only to a limited extent in older and more woody roots, and, according to W. Merz, is almost entirely absent during summer. The following analyses of air-dry belladonna roots are due to E. M. Holmes:—

	Woody Roots.	Soft Roots.
Moisture, ...	7·94 per cent.	10·28 per cent.
Soluble ash, ...	3·43 ,,	2·20 ,,
Insoluble ash, . . .	4·60 ,,	3·68 ,,
Alcoholic extract, . .	22·53 ,,	29·87 ,,
Aqueous extract, . .	15·96 ,,	10·50 ,,

Belladonna *leaves* contain cellulose, chlorophyll, alkaloidal salts, fatty and resinous matters, &c. Choline is present, and, according to Biltz, asparagin sometimes crystallises from the extract after long keeping, but the crystals observed by Attfield consisted of potassium nitrate and chloride. By dialysis, Attfield isolated potassium nitrate, and square prisms of an organic salt of magnesium. Kunz found 0·6 per cent. of succinic acid in an extract prepared from the herbaceous parts of belladonna. Flückiger found the ash of dry belladonna leaves to amount to 14·5 per cent., and to consist chiefly of the carbonates of calcium and the alkali-metals.

With regard to the *alkaloids* of belladonna, O. Hesse (*Annalen*, cclxi. 87) states that in his experience the herb of cultivated belladonna contains atropine almost exclusively, but that it is associated with other alkaloids in the leaves of wild plants, and especially in the roots of both kinds. In an old root, Hesse found much hyoscyamine but no atropine. E. Schmidt (*Pharm. Zeit.*, 1889, page 583) found hyoscyamine but no atropine in full grown roots which had been kept for years. In roots of one year's growth he found both atropine and hyoscyamine, but the latter alkaloid only in fresh old roots. The leaves of wild belladonna contained much hyoscyamine and a little atropine, while the ripe berries contained atropine only. E. Schmidt has found both hyoscyamine and hyoscine in *Scopolia atropoïdes* and *Scopolia japonica*,[1] and traces of an alkaloid having a mydriatic action in *Solanum tuberosum*, *S. nigrum* and *Lycium barbarum*. Mandragorine, the alkaloid of *Mandragora vernalis*, is mydriatic and possibly isomeric with atropine (page 243).

crystalline residue with cold ether, chrysatropic acid remained, while leucotropic acid, $C_{17}H_{22}O_5$, dissolved. The latter is a bitter substance, crystallising in microscopic prisms which melt at 74°.

[1] Dunstan and Chaston found the alkaloid of *Scopolia carniolica* to consist of hyoscyamine with a possible traces of hyoscine.

A. W. Gerrard (*Year-Book Pharm.*, 1881, 1882, 1884) has published a number of valuable observations on belladonna, in which he found the following percentages of alkaloid:—

Age of Plant.	*Wild Plant.*		*Cultivated Plant.*	
	Root.	*Leaves.*	*Root.*	*Leaves.*
Two years,	·260	·431	·207	·320
Three years,	·381	·407	·370	·451
Four years,	·410	·510	·313	·491

These and other observations of Gerrard show that the leaf of belladonna is the part of the plant richest in alkaloid; the root, fruit, and stem coming next in the order stated.[1] The results of A. B. Lyons (*Manual of Pharmaceutical Assaying*) do not show the same distinction, for in twelve samples of (air-dried) *leaves* the proportion of alkaloids varied from 0·41 to 0·69 per cent., and in fifteen samples of *roots* from 0·47 to 1·35 per cent. The extractive matter in the leaves (air-dried, and treated with 66 per cent. alcohol) ranged from 6·6 to 12·1 per cent., and in the roots from 22·5 to 31·5 per cent., with an average of about 8 per cent. of moisture. Lyons states that the pressed leaves do not suffer deterioration when kept for six years.

R. Kordes found 0·58, and von Gunther 0·83 per cent. of alkaloid in belladonna leaves, while Lefort gives the average yield from 8 specimens at 0·436 per cent.

As the general result of published investigations, Farr and Wright state that the proportion of alkaloids in good specimens of commercial belladonna leaves ranges from 0·30 to 0·87 per cent., their own experiments varying between 0·30 and 0·90, with an average of 0·49 per cent. German leaves are distinctly poorer in alkaloid and extractive matter than those of English growth, and hence the *B.P.* direction to prepare the tincture from the leaves of "plants grown in Britain" should be strictly observed. As one part of belladonna leaves produces 20 parts of the *B.P. tincture*, it follows that the proportion of alkaloid in this preparation averages 0·025 per cent., which strength might advantageously be adopted as a standard.

For the assay of belladonna *root*, Dunstan and Ransom (*Pharm. Jour.*, [3], xiv. 623) recommend extraction in the

[1] The influence of age on the proportion and nature of the alkaloids of belladonna has also been studied by Schütte (*Pharm. Jour.*, [3], xxii. 429).

following manner:—20 grammes of the dry and finely-powdered root is extracted by hot percolation with a mixture of equal volumes of chloroform and absolute alcohol.[1] If an extraction-apparatus be used about 60 c.c. of the mixture will be required. The solution is agitated with two successive quantities of distilled water, using 25 c.c. each time. The separation of the aqueous liquid from the chloroform occurs promptly and completely on warming the liquid slightly. The chloroform retains nearly the whole of the colouring-matter, while the alcohol and alkaloids (as salts) pass into the water.[2] The aqueous layer is separated, and agitated once with chloroform to remove the last traces of colouring-matter; after which it is rendered alkaline with ammonia, and agitated twice with chloroform, using 25 c.c. each time, to extract the alkaloid. The separated chloroform is agitated once with water rendered faintly alkaline with ammonia, and then evaporated, the residue being dried at 100° till constant in weight. The alkaloid thus isolated is obtained as a perfectly transparent fused mass. It is soluble in water, and the aqueous solution gives precipitates with Thresh's, Mayer's, and Sonnenschein's reagents (pages 136, 138). It gives a faint white precipitate with mercuric chloride, and a copious white precipitate with gallotannic acid cautiously added. This last precipitate is *very readily* soluble in a slight excess of the reagent, a distinct trace, however, invariably remaining undissolved (Farr and Wright).[3]

Instead of weighing the isolated alkaloid it may be titrated with standard acid and litmus (or methyl-orange) as recommended by Gerrard (*Year-Book Pharm.*, 1884, page 447).

Dunstan and Ransom (*Year-Book Pharm.*, 1885, page 391) recommend continuous percolation with boiling absolute alcohol for the extraction of the alkaloids from belladonna *leaves*, and they proved that the leaves thus treated yielded no further

[1] Chloroform alone extracts the alkaloids very incompletely. Alcohol employed alone dissolves much extractive matter which impedes the subsequent extraction and purification of the alkaloids. If rectified spirit instead of absolute alcohol be employed in admixture with chloroform, the water present causes swelling of the material, and the progress of the extraction is seriously impeded. Dunstan and Ransom proved that the mixture of equal measures of chloroform and alcohol recommended by them completely extracted belladonna root, and that pure atropine was not appreciably affected by prolonged boiling with the solvent.

[2] Although Dunstan and Ransom found the whole of the alkaloids to pass into the aqueous liquid, A. B. Lyons points out that it is desirable, as a precaution, to make a small addition of sulphuric acid to the water employed.

[3] The alkaloids from stramonium behave similarly, probably owing to the presence of a small quantity of another (third ?) alkaloid.

quantity of alkaloid when boiled with dilute hydrochloric acid, or when mixed with lime and extracted with chloroform. From the extract obtained on evaporating the alcoholic liquid, they found it impossible to remove the whole of the alkaloid, even by many successive treatments with water or dilute hydrochloric acid. They therefore recommend that the alcoholic liquid should be diluted considerably with water acidulated with hydrochloric acid, and the liquid then shaken repeatedly with chloroform to remove the chlorophyll and fat.[1] From the liquid thus purified the alkaloids can readily be obtained pure by adding excess of ammonia and extracting with chloroform.

A modification of the foregoing process is recommended by Dunstan and Ransom for the assay of the *solid extract* of belladonna. Two grammes should be warmed with dilute hydrochloric acid until as much as possible is dissolved, when the liquid is filtered through cotton or glass wool, and the residue well washed with hot dilute hydrochloric acid. The filtrate is repeatedly shaken with chloroform to remove chlorophyll, then ammonia added, and the liberated alkaloids extracted with chloroform.

The *tincture* of belladonna can also be assayed by the foregoing process after evaporating off the greater part of the alcohol,[2] and the same remark applies to the *fluid extract*. It is, however, in many cases preferable to treat the clear liquid at once with ammonia and chloroform. On subsequently treating the separated chloroform with dilute sulphuric acid, the colouring-matters remain in

[1] J. Williams suggests that it would be better to employ ether at this stage of the process.

[2] Farr and Wright have shown that the strength of alcohol used in exhausting the drug has little effect on the proportion of alkaloid in the tincture, though it very greatly affects the proportion of mucilaginous and colouring matters extracted, and the former of these impede the separation of the chloroformic and aqueous layers. The difficulty may be overcome by evaporating the tincture to a syrup and treating it with strong alcohol, which precipitates the mucilage, and the filtrate gives on evaporation a liquid which can be readily dealt with.

Farr and Wright find it impossible to remove the whole of the alkaloids of belladonna (and henbane) by repeated agitation with ether in presence of ammonia, at least 20 per cent. of the total remaining unextracted by ether, but recoverable by subsequent agitation with chloroform. Hence ether is an unsuitable solvent for extracting mydriatic alkaloids, and the results of Gerrard and others who have used it are probably below the truth. In fact, Gerrard himself states that several extractions with ether are necessary, and that, as a rule, he subsequently renders the ammoniacal solution neutral with citric or tartaric acid, evaporates it to a small volume, treats it again with ammonia, and again agitates with ether.

the chloroform, while the alkaloids can be recovered in the pure state by rendering the acid liquid again alkaline, and agitating it with chloroform.

A. W. Gerrard has employed substantially the same process as the above for the assay of the root and leaves of *henbane* (*Pharm. Jour.*, [3], xxi. 212; xxii. 213). The substance is dried at 100°, powdered, and exhausted with proof-spirit. The spirit is distilled off, and the semi-fluid extract treated with water containing 1 per 1000 of hydrochloric acid, filtered, and the filtrate further diluted to 100 c.c. The alkaloids are extracted by ammonia and chloroform in the usual way, purified by solution in ether, and agitated with hydrochloric acid; again liberated by ammonia, extracted by ether, and determined in the alkaloidal residue by titration with decinormal hydrochloric acid. The following results are recorded:—

Variety of Henbane.	Part Used.	Where Grown.	Yield of Alkaloids per 1000.
Biennial, . .	Roots.	Middlesex.	1·602
,, . .	,,	Sussex.	1·550
,, . .	,,	Lincolnshire.	1·729
,, . .	First year's leaf.	Lincolnshire.	·690
,, . .	,,	Sussex.	·667
,, . .	,,	Middlesex.	·592
,, . .	Second year's leaf,	Middlesex.	·672
,, . .	,,	Sussex.	·680
,, . .	,,	Lincolnshire.	·656
Annual, . .	Leaves and tops.	Leicestershire.	·641
,, . .	,,	Surrey.	·659
,, . .	,,	Middlesex.	·701
Annual, . .	Entire herb.	Germany.	·295
Biennial, . .	First year's leaves.	France.	·398
,, . .	,, (old).	England.	·390
,, . .	Second year's tops (old).	England.	·451

Gerrard's experiments appear to show that a considerable falling off in the alkaloidal value of the leaves occurs with age. He considers that bright-coloured, well-preserved henbane, whether annual or biennial, can be relied on to yield good preparations, while old and dark-coloured leaves, containing stalks and fruit, should be avoided. He regards the first year's root of biennial *Hyoscyamus niger* as much richer in alkaloids than the herbaceous portions of the plant, but both as much poorer than the respective parts of belladonna.[1] *Hyoscyamus albus* is much used in the south of Europe, but no greater strength is attributed to it.

[1] These conclusions are entirely in opposition to the experience of E. Thorey (Dragendorff's *Quelques Drogues Actives*), who found henbane to contain alkaloid in greatest quantity in the leaves, next in the fruit, then in the roots, and lastly in the stalk. The substance was first exhausted with petroleum spirit to free it from fat, then dried, finely powdered, and extracted

F. Ransom found 0·58 per 1000 of pure alkaloid in the seeds of biennial henbane grown at Hitchin. Henbane seed is used in Germany for the preparation of the alkaloid.

Farr and Wright (*Pharm. Jour.*, [3], xxii. 255) have proved that practically the whole of the alkaloid of *henbane* is contained in the *tincture*. From 100 c.c. of tincture (corresponding to 12·5 grammes of the substance), prepared from different parts of the plant, they obtained the following weights of alkaloid :—

	From 100 c.c. of Tincture.	From 100 parts of Substance.
Dried leaves, average, .	0·0103 grammes.	0·0824 per cent.
Recently dried fresh leaves,	0·013 ,,	0·104 ,,
Seeds, ...	0·015 ,,	0·120 ,,
Root-bark, ...	0·020 ,,	0·160 ,,

From *stramonium seeds*, J. D. A. Hartz (*Pharm. Jour.*, [3], xv. 203) obtained 0·167 per cent. of alkaloid, by extracting the fat from the dried substance by petroleum spirit, then removing the alkaloid with proof-spirit, and proceeding in the usual way. Farr and Wright found from 0·16 to 0·24 per cent. of alkaloid in stramonium seeds. E. Schmidt found, in four samples of stramonium *seed* from different sources, 0·25, 0·37, 0·05, and 0·20 per cent. of total alkaloids. From 50 to 70 per cent. of these consisted of pure atropine melting at 115° C. The remainder, which was much more difficult to crystallise, consisted of hyoscyamine, and probably other bases and their decomposition-products. But the relative proportions of the alkaloids are probably very variable, as

with faintly acidified rectified spirit at a temperature of 30°–40° C. The alcohol was distilled off, and the residual liquid filtered. The filtrate was purified by agitation with chloroform or petroleum spirit, then rendered alkaline with potash or ammonia, and the alkaloid extracted by agitation with chloroform. The following figures, by Thorey, represent the percentage proportions of alkaloids obtained from the dried materials :—

art of Plant.	Plant destitute of Flowers.				Plant in Flower.				Plant in Fruit.		
	Hyosc. albus.		Hyosc. niger.		Hyosc. albus.		Hyosc. niger.		Hyosc. albus.		Hyosc. n
	1868.	1869.	1868.	1869.	1868.	1869.	1868.	1869.	1868.	1869.	1868.
eds, .	...	...	...	...	...	...	...	...	0·162	0·172	0·075
aves, .	0·588	0·469	0·154	0·192	0·359	0·329	0·147	0·206	0·211	0·158	0·065
alk, .	0·012	...	0·070	0·017	0·036	0·048	0·032	0·030	0·027	0·029	0·009
ot, .	0·128	0·176	0·027	0·080	0·146	0·262	0·127	0·138	0·106	0·086	0·028

Ladenburg found hyoscyamine to preponderate, and Schütte found that both fresh and old stramonium seeds yielded chiefly hyoscyamine, with small quantities of ready-formed atropine and scopolamine. A. B. Lyons (*Manual of Pharmaceutical Assaying*) found in five specimens of *stramonium seed* proportions of alkaloid (titrated by Mayer's solution) ranging from 0·45 to 0·55 per cent., the extractive matter yielded to strong alcohol by the same samples varying from 3·3 to 7·5 per cent. In eight samples of *stramonium leaves*, Lyons found from 0·40 to 0·52 per cent. of alkaloid (titrated), and from 19·5 to 25·3 per cent. of extractive matter yielded to spirit of 66 per cent. Farr and Wright extracted from 0·12 to 0·22 per cent. of alkaloid from stramonium leaves.

R. Kordes ("Inaugural Dissertation," Dorpat, 1888) found the following percentages of alkaloid in the sources stated :—

	Leaves.	*Roots.*
Belladonna, ...	0·64 per cent.	0·74 per cent.
Hyoscyamus, ...	0·15 ,,	0·13 ,,
Stramonium, ...	0·20 ,,	0·15 ,,

R. Kordes has also published the results of analyses of a large number of *extracts* of belladonna, henbane and stramonium.[1] His figures show the yield of extract, the percentage of water and alkaloid in the preparation, and the proportion of total alkaloid obtained in the extract.

Dunstan and Ransom (*Pharm. Jour.*, [3], xvi. 777) found the alkaloids in nine commercial specimens of *solid extract of belladonna root* to vary from 1·65 to 4·45 per cent., the water ranging from 16·0 to 21·6 per cent. They state that the extract contains, besides atropine and hyoscyamine (and possible traces of another alkaloid), the fluorescent substance called chrysatropic acid (page 262) and "much dextrose." This observation is of interest in relation to the assumption of Schweissinger (*Pharm. Zeit.*, 1886, page 101), that a genuine *extract of belladonna leaves* contains no substance capable of reducing Fehling's solution at a temperature of 60°–70° C., any reddish turbidity or precipitate being probably due to sophistication with dextrin or the extract of dulcamara or taraxacum. Analyses of various extracts of belladonna have been published by J. C. Umney (*Pharm. Jour.*, [3], xxii. 364).

L. van Itallie recommends that the *extracts of belladonna* and *henbane* should be assayed by treating 5 grammes of the sample with 10 drops of dilute sulphuric acid (1:20), diluting with water to 50 c.c., and macerating for some hours. Twenty-five c.c. of a 10 per

[1] Also analyses of extracts of conium, cheledonium, aconite, nux vomica and physostigma.

cent. solution of lead acetate is then added, and after allowing the precipitate to settle the liquid is passed through a dry filter. From 50 c.c. of the filtrate the excess of lead is precipitated by 10 c.c. of dilute sulphuric acid (1:10), and the liquid again filtered. From 50 c.c. of this second filtrate the alkaloids are then liberated by ammonia, extracted by three agitations with chloroform, the solvent evaporated, and the residual alkaloids dissolved in spirit and titrated with centinormal acid.

COCA ALKALOIDS.[1]

The leaves of *Erythroxylon coca* and allied species[2] contain a number of closely-allied alkaloids, all of which appear to be derivatives of ecgonine, $C_9H_{15}NO_3$, a base which Einhorn and Hesse regard as a derivative of tetrahydropyridine (pages 106, 164), and to which they assign a constitution expressed by the following formula:—

$$CH_2\left\{\begin{matrix} CH_2.CH[CH(OH)CH_2.CO.OH] \\ CH{:}CH \end{matrix}\right\}N.CH_3$$

According to this formula, ecgonine is methyltetrahydropyridyl-β-hydroxypropionic acid. When heated with baryta, it splits into carbon dioxide and isotropine, and hence may be regarded as isotropyl-carboxylic acid.

$$\underset{\text{Ecgonine.}}{Me.C_5H_7N.CH(OH).CH_2.COOH} = CO_2 + \underset{\text{Isotropine.}}{Me.C_5H_7N.CH(OH).CH_2.H}$$

The relation between ecgonine and isotropine (and therefore between cocaine and atropine) is equally evident from a comparison of the formula of their respective anhydrides:—

$$\underset{\text{Anhydro-ecgonine.}}{MeN\left\{\begin{matrix} .CH.(CH{:}CH.COOH).CH_2. \\ .CHCH_2. \end{matrix}\right\}} \quad \underset{\text{Tropidine.}}{MeN\left\{\begin{matrix} .CH.(CH{:}CH_2).CH_2. \\ .CH{:}CH.CH_2. \end{matrix}\right\}}$$

The hydrogen of the hydroxyl-group of ecgonine can be substituted by acetyl, benzoyl, cinnamyl, and other acid-radicals. Thus:—

Benzoyl-ecgonine, $Me.C_5H_7N.CH(O.C_7H_5O).CH_2.COOH$
Cinnamyl-ecgonine, $Me.C_5H_7N.CH(O.C_9H_7O).CH_2.COOH$

[1] The author is indebted to Dr B. H. Paul and Mr A. J. Cownley for perusal and correction of this section.

[2] Upwards of eighty species of the genus *Erythroxylon* are found in Brazil (*Pharm. Jour.*, [3], xvii. 507); but most of these species, other than *E. coca*, yield very little cocaine (*Pharm. Jour.*, [3], xix. 70).

By heating those compounds with alkyl iodides, the corresponding esters may be obtained:—

Methyl benzoyl-ecgonine (cocaine),	$MeC_5H_7N.CH(O.C_7H_5O).CH_2.CO.OCH_3$
Ethyl benzoyl-ecgonine (homococaine),	$MeC_5H_7N.CH(O.C_7H_5O).CH_2.CO.OC_2H_5$
Methyl cinnamyl-ecgonine, . .	$MeC_5H_7N.CH(O.C_9H_7O).CH_2.CO.OCH_3$

Methyl benzoyl-ecgonine or cocaine is the most important and characteristic of the bases of coca. Methyl cinnamyl-ecgonine occurs occasionally, in small quantity, in the broad-leaved South American coca, and regularly, and sometimes in considerable quantity, in Truxillo coca.

When dibasic acids react on ecgonine, bodies of more complex constitution result. One of these (the methyl-ester of a substance polymeric with cinnamic acid, called by Hesse cocaic acid, $C_{18}H_{16}O_4$, and by Liebermann γ-isatropic or truxillic acid), is the cocamine, $C_{38}H_{46}N_2O_8$, of Hesse, and the isatropyl-cocaine or α-truxilline of Liebermann. The next higher homologue of cocayl-ecgonine methyl-ester also appears to exist in coca, as also the corresponding derivatives of iso-cocaic (*β-truxillic*) and homo-isococaic acids.

The following is a list of the bases hitherto detected in coca leaves. The amorphous base to which Hesse gave the name of cocaïdine has been proved to be a mixture; and the volatile base called hygrine by Lossen has not since been obtained.

$C_9H_{17}NO_2$,	Anhydro-ecgonine,	$C_8H_{13}N\left\{\begin{matrix}O\\CO\end{matrix}\right\}$; or $MeC_5H_7N.CH{:}CH.COOH$
$C_9H_{15}NO_3$,	Ecgonine, . .	$C_8H_{13}N\left\{\begin{matrix}OH\\CO.OH\end{matrix}\right.$
$C_{16}H_{19}NO_4$,	Benzoyl-ecgonine,	$C_8H_{13}N\left\{\begin{matrix}O.C_7H_5O\\CO.OH\end{matrix}\right.$
$C_{17}H_{21}NO_4$,	Benzoyl-ecgonine methyl-ester (cocaine),	$C_8H_{13}N\left\{\begin{matrix}O.C_7H_5O\\CO.OCH_3\end{matrix}\right.$
$C_{18}H_{21}NO_4$,	*Cinnamyl-ecgonine,*	$C_8H_{13}N\left\{\begin{matrix}O.C_9H_7O\\CO.OH\end{matrix}\right.$
$C_{19}H_{23}NO_4$,	Cinnamyl-ecgonine methyl-ester,	$C_8H_{13}N\left\{\begin{matrix}O.C_9H_7O\\CO.OCH_3\end{matrix}\right.$
$C_{38}H_{46}N_2O_8$,	Cocayl - ecgonine methyl-ester (cocamine),	$\left.\begin{matrix}C_8H_{13}N(CO.OCH_3)O\\C_8H_{13}N(CO.OCH_3)O\end{matrix}\right\}C_{18}H_{14}O_2$
$C_{40}H_{50}N_2O_8$,	Homococamine,	$\left.\begin{matrix}C_8H_{13}N(CO.OCH_3)O\\C_8H_{13}N(CO.OCH_3)O\end{matrix}\right\}C_{18}H_{12}(CH_3)_2O_2$
$C_{17}H_{19}NO_2$,	Benzoyl-pseudo-tropine,	$C_8H_{14}NO(C_7H_5O)$

Isomerides of cocamine and homococamine probably exist in coca, as Hesse has isolated from the products of hydrolysis iso-

cocaic and homo-isococaic acids. Similarly, Liebermann has isolated two isomers of cinnamic acid, isocinnamic and allocinnamic acids, from the products of the decomposition of coca bases.

With the exception of ecgonine and anhydro-ecgonine, all the bodies in the foregoing list are saponifiable, splitting up when heated to 80°–100° with hydrochloric acid, or when boiled with alcoholic potash, according to the following equations:—

1. a. $C_{17}H_{21}NO_4 + H_2O = C_{16}H_{19}NO_4 + CH_4O$
   Cocaine. — Benzoyl-ecgonine. — Methyl alcohol.

   b. $C_{16}H_{19}NO_4 + H_2O = C_9H_{15}NO_3 + C_7H_6O_2$
   Benzoyl-ecgonine. — Ecgonine. — Benzoic acid.

2. a. $C_{19}H_{23}NO_4 + H_2O = C_{18}H_{21}NO_4 + CH_4O$
   Cinnamyl-ecgonine methyl-ester. — Cinnamyl-ecgonine. — Methyl alcohol.

   b. $C_{18}H_{21}NO_4 + H_2O = C_9H_{15}NO_3 + C_9H_8O_2$
   Cinnamyl-ecgonine. — Ecgonine. — Cinnamic acid.

3. a. $C_{38}H_{46}N_2O_8 + 3H_2O = C_9H_{15}NO_3 + C_{27}H_{29}NO_6 + 2CH_4O$
   Cocamine (truxilline). — Ecgonine. — Ecgonyl-cocaic acid. — Methyl alcohol.

   b. $C_{27}H_{29}NO_6 + H_2O = C_9H_{15}NO_3 + C_{18}H_{16}O_4$
   Ecgonyl-cocaic acid. — Ecgonine. — Cocaic acid (α-truxillic acid).

4. $C_{17}H_{19}O_2 + H_2O = C_{18}H_{15}NO + C_7H_6O_2$
   Benzoyl-pseudotropine. — Pseudotropine. — Benzoic acid.

From these equations it is evident that the simpler bases of coca are decomposition-products of the natural alkaloids cocaine, cocamine, homococamine, and cinnamyl-ecgonine methyl-ester (cinnamyl-cocaine), all of which readily undergo hydrolysis with formation of ecgonine, methyl alcohol, and an aromatic acid. Benzoyl-pseudotropine differs from the other bases of coca by yielding no methyl alcohol on hydrolysis.

It is evident that the mixed alkaloids of coca will consist of the various natural bases in indefinite proportion, contaminated by the products of their decomposition. Hence the separation o pure cocaine from the co-existing bases is very troublesome. The difficulty has been overcome by Liebermann and Giesel (*Ber.*, xxi. 3196) in an interesting and ingenious manner, which allows of the utilisation of the valueless and troublesome amorphous bye-products, which are to be had in considerable quantity. The process consists in boiling the mixed bases with hydrochloric acid, whereby they all suffer hydrolysis, with formation of ecgonine; and this base forms the starting-point for the subsequent synthesis

of cocaine by Einhorn's method (*Ber.*, xxi. 3335). Thus by passing dry hydrochloric acid gas into a solution of ecgonine hydrochloride in methyl alcohol until the solution has become cold, and then boiling the liquid for an hour under an inverted condenser, the hydrochloride of ecgonine methyl-ester is formed, which on concentrating the alcoholic solution crystallises in prisms, melting with decomposition at 212°. Cocaine is formed when this compound is heated on the water-bath with an equal weight of benzoyl chloride until the mixture becomes homogeneous and the evolution of hydrochloric acid ceases. The hot melted mass is poured into water, separated from the precipitated benzoic acid, and the cocaine precipitated by ammonia or an alkaline carbonate, and recrystallised from alcohol. An alternative method is to convert the ecgonine into the benzoyl-derivative, and treat a solution of the latter body in methyl alcohol with hydrochloric acid gas. The artificial cocaine prepared by either of these methods possesses all the characters of the natural alkaloid.

Cocaine. Benzoyl methyl-ecgonine. Methyl benzoyl-ecgonine.

$$C_{17}H_{21}NO_4;\ \text{or}\ C_5H_7(CH_3)N.CH\begin{cases} O.CO.C_6H_5 \\ CH_2.CO.OCH_3 \end{cases}$$

Cocaine is the characteristic alkaloid of coca leaves, and has recently acquired a place in the first rank of alkaloids of medicinal value. It may be extracted from the plant by the usual processes, avoiding as much as possible treatment with acids and alkalies, as it undergoes hydrolysis with great facility with formation of objectionable decomposition-products.

The synthesis of cocaine was effected by Merck by treating together ecgonine, benzoic anhydride and methyl iodide to 100° for ten hours in a sealed tube. The industrial reproduction of cocaine from ecgonine has been effected and patented by Liebermann (page 272).

Cocaine crystallises from a strong alcoholic solution in colourless monoclinic prisms, melting at 97°–98° C., and subliming with partial decomposition at a higher temperature.

Cocaine is very slightly soluble in water,[1] but dissolves readily in alcohol, ether, chloroform,[2] benzene, petroleum spirit, carbon

[1] The solubility of cocaine in cold water is probably near to 1 in 1300 (B. H. Paul), but is commonly greatly over-estimated, owing to the ease with which cocaine is decomposed by hot water with formation of soluble products.

[2] The solubility of cocaine in chloroform enabled B. H. Paul to separate it from morphine, and prove a product introduced under the name of hopeine, and said to be a natural narcotic alkaloid from American hops, to be, in fact, an artificial mixture of cocaine and morphine (*Pharm. Jour.*, [3], xvi. 877).

disulphide and volatile and fixed oils. It is readily removed from its solutions by adding ammonia and agitating with ether or other immiscible solvent.

An aqueous solution of cocaine has a strong alkaline reaction to litmus and methyl-orange, but does not affect phenolphthaleïn. The free base may be titrated with the aid of either of the former indicators. An aqueous solution of cocaine, if not very carefully prepared and secluded from air, or preserved by an antiseptic, rapidly decomposes with formation of vegetable growths.

Cocaine produces on the tongue a sudden and characteristic cessation of feeling, which lasts only a few minutes. One drop of a 4 per cent. solution (of the hydrochloride), if placed on the tongue, soon produces a decided numbness, the effect being evanescent unless the application be repeated. Cocaine also produces an intense local anæsthetic and blanching effect on the mucous membrane. A single drop of a 4 per cent. solution suffices to blanch the conjunctiva of the eye. Anæsthesia of the eye, of much value in ophthalmic operations, can be produced by a somewhat larger dose. Dilation of the pupil is generally produced by cocaine, whether applied locally to the eye or otherwise introduced into the system; but the mydriasis produced by cocaine is not so invariable and is far less intense than that characteristic of atropine and its isomers.

In large doses, cocaine has marked poisonous properties. The fatal dose for dogs is from 2 to 5 grains. The hypodermic injection of $\frac{1}{20}$ grain has caused dangerous symptoms in a girl twelve years of age (see *Pharm. Jour.*, [3], xvi. 721).[1]

Cocaine is lævo-rotatory, the specific rotation in chloroform solution being about $-15^\circ{\cdot}8$ for the sodium ray; while the rotation of the hydrochloride in dilute alcohol is $-52^\circ{\cdot}2$.

Reactions of Cocaine.

Cocaine is precipitated from its solutions by caustic alkalies, alkaline carbonates and ammonia. It is almost insoluble in excess of ammonia, which is to be preferred as a precipitant.[2] Precipitated cocaine is amorphous when thrown down from strong solutions, but rapidly becomes crystalline.

[1] For various alarming symptoms produced by cocaine in dental practice, see remarks by Stockman (*Pharm. Jour.*, [3], xviii. 791). A resumé of the pharmacology of cocaine and its allies appeared in the *Pharmaceutical Journal*, [3], xxi. 161.

[2] If a solution of cocaine salt be precipitated with caustic soda or sodium carbonate, the filtrate will be found to contain a distinct trace of benzoic acid resulting from decomposition of the alkaloid; but this is not the case if ammonia be substituted (B. H. Paul).

Mayer's solution precipitates cocaine from extremely dilute solutions, and A. B. Lyons has attempted to employ the reaction for the determination of cocaine, but with results which are wanting in exactness.

Iodised iodide of potassium gives a rose-coloured precipitate with a solution of 1 part of cocaine hydrochloride in 7,500 of water; in stronger solutions the precipitate appears brown, and under the microscope assumes the form of black globules.

Tannin produces a distinct cloud in neutral solutions of cocaine containing 1 : 25,000, and a distinct precipitate with twice that proportion. Picric acid produces in strong solutions a yellow precipitate, rapidly becoming crystalline, and appearing under the microscope in sheaf-like forms. Phosphomolybdic acid produces a faint turbidity in solutions of 1 : 50,000, and a distinct precipitate with 1 : 12,500. Phosphotungstic acid gives a gelatinous white precipitate, soluble in ammonia.

Platinic chloride produces at once, in solutions of cocaine hydrochloride containing 1 : 400, a yellow precipitate consisting of plumose needles, mostly of stellate pattern. In solutions of 1 : 600 most of the crystals resemble carpet-tacks, consisting of short, well-formed prisms, with a single branch from the centre, joined at an oblique angle and tapering to a point. The characters of the chloroplatinate distinguish cocaine from the amorphous base associated with it in coca-leaves, the platinum salt of which is far less soluble in water, and crystallises in rosette-like forms, contrasting strongly with the feathery appearance of the cocaine salt.

Cocaine aurochloride is precipitated on adding auric chloride to a solution of cocaine hydrochloride. In solutions containing 1 : 3000 an immediate precipitate is produced, which appears under the microscope in forms resembling fern-fronds, generally with a stellate arrangement. In solutions of 1 : 12,000 similar crystals form after a short time. "Cocaïdine" aurochloride forms minute prismatic crystals, having a microscopic appearance quite different from that of the cocaine salt (A. B. Lyons, *Amer. Jour. Pharm.*, lvii. No. 10).

Cocaine readily precipitates prussian blue from a mixture of solutions of potassium ferricyanide and ferric chloride.

According to Lerch and Schärges, if a drop of ferric chloride be added to a solution of cocaine and the liquid boiled, an intense red colour will be developed "owing to the formation of benzoic acid." Benzoyl-ecgonine also gives the reaction.

Potassium bichromate does not precipitate cocaine except from neutral solutions, unless they are very concentrated (1:25); but Metzer states that from a solution containing hydrochloric acid, chromic acid precipitates the chromate, $C_{17}H_{21}NO_4,H_2CrO_4$, in

silky, lustrous plates (compare page 287). If 0·05 gramme of cocaine hydrochloride be dissolved in 5 c.c. of water, and five drops of a 5 per cent. aqueous solution of chromic acid added, each drop produces a distinct precipitate, which immediately redissolves; but if 1 c.c. of strong hydrochloric acid be now added, a heavy yellow precipitate of cocaine chromate is produced. If cocamine be present, reduction of the chromic acid will ensue. Ecgonine, sparteine, atropine, caffeine, pilocarpine, codeine and morphine do not form yellow precipitates with chromic acid or potassium chromate. Quinine, quinidine, cinchonine, cinchonidine, hydroquinine, apomorphine, brucine, strychnine and veratrine form precipitates with 5 per cent. chromic acid if the solutions are neutral; but, according to K. Metzer (*Pharm. Zeit.*, xxxiv. 697), cocaine is singular in being precipitated only after addition of hydrochloric acid.

F. Giesel (*Pharm. Zeit.*, 1886, page 132) has observed that cocaine permanganate is very stable compared with the corresponding salts of the majority of alkaloids. Hence, if 1 centigramme of cocaine hydrochloride be dissolved in one or two drops of water, and about 1 c.c. of a 3 per cent. solution of potassium permanganate be added, a purple-violet crystalline precipitate of cocaine permanganate is produced, the supernatant liquid acquiring a purple-violet tint. A. B. Lyons recommends that a strong solution of the cocaine salt should be used, and the permanganate employed in decinormal solution (3·162 grammes per litre). The precipitate is unstable, and decomposes in a few hours even at the ordinary temperature, leaving a brown hydrated manganese dioxide. If the liquid containing the precipitate be heated to boiling decomposition occurs at once, but without the production of any peculiar odour. But if examined under the microscope when first thrown down, the precipitate is found to consist, wholly or in part, according to the strength of the cocaine solution, of translucent, violet-red, rhombic (nearly rectangular) plates of great beauty, often grouped together to form rosettes. A 5 per cent. solution of cocaine gives a copious precipitate at once, and a 2 per cent. solution after a short time; but with a 1 per cent. solution the crystals only form as evaporation takes place.

The behaviour with potassium permanganate serves to detect an admixture of methyl cinnamyl-ecgonine and certain other impurities in cocaine hydrochloride. The presence of these causes an immediate reduction of the permanganate in the cold. The first drop or two of the reagent produces a brown discoloration, while the precipitate thrown down by a further addition is more or less brown, instead of a distinct violet-purple or red. If a limited quantity of the reagent be employed, and the liquid heated to

boiling, in presence of impurities a distinct odour will be developed in some cases resembling that of bitter-almond oil, and in others like that of crude cocaine (A. B. Lyons, *Amer. Journ. Pharm.*, 1886, page 240). The behaviour of other alkaloids with potassium permanganate is described on page 144.

According to F. da Silva (*Compt. Rend.*, cxi. 348; *Pharm. Jour.*, [3], xxi. 162), when treated by Vitali's test for atropine (page 257), even a minute quantity of cocaine (0·0005 gramme) developes a distinct and peculiar odour, recalling that of peppermint or citronella. No other alkaloid extracted by benzene from an ammoniacal solution behaves at all similarly, though atropine, hyoscyamine, strychnine, codeine and eserine give colour-reactions, and the last-named alkaloid developes a disagreeable smell resembling phenyl-carbamine (page 46). Delphinine, brucine, and veratrine develop slight odours which cannot be mistaken for that produced by cocaine. A. C. Stark (*Pharm. Jour.*, [3], xxi. 848) has confirmed Da Silva's statements, but considers the odour scarcely distinctive enough to render the test completely reliable.

SALTS OF COCAINE.

Cocaine Hydrochloride. Hydrochlorate of Cocaine. $C_{17}H_{21}NO_4,HCl$. This salt, which is readily prepared by neutralising cocaine by hydrochloric acid, crystallises from alcohol in short prisms melting at 181°·5. The crystals from the aqueous solution contain, according to A. B. Lyons, 9·6 per cent. of water, while those from the alcoholic solution are anhydrous. The salt is not hygroscopic, but is soluble in less than its own weight of water, forming a thick syrupy liquid. It is readily soluble in spirit, but with less facility in absolute alcohol, chloroform, and amylic alcohol; and is practically insoluble in ether, petroleum spirit, and fixed and volatile oils. Ether precipitates cocaine hydrochloride from its solutions in absolute alcohol[1] and chloroform.

Cocaine Hydrobromide, $BHBr,2H_2O$, crystallises readily from its aqueous solution in transparent prisms, stable in the air.

Cocaine Acetate is readily soluble in water. It is difficult to obtain it in a crystalline condition, as acetic acid is given off during the evaporation of its solution.

Cocaine Oleate readily crystallises, and is soluble in oleic acid and fixed oils.

Cocaine gives crystalline salts with sulphuric, boric and oxalic acids. The *citrate* is hygroscopic, and crystallises with difficulty.

[1] Stockman (*Pharm. Jour.*, [3], xvii. 862) gives the solubility of pure cocaine hydrochloride in chloroform, absolute alcohol, and amylic alcohol as 1 in 48, 1 in 34, and 1 in 70 respectively; but B. H. Paul does not find such large proportions of solvent necessary.

Cocaine Benzoate, $C_{17}H_{21}NO_4,C_7H_6O_2$, may be prepared by mixing molecular proportions of cocaine and benzoic acid. It is a very soluble salt, obtainable with difficulty in acicular crystals, the solution usually drying up to a gummy mass, which gradually acquires a crystalline structure. A sample of commercial cocaine benzoate of French origin was found by B. H. Paul to give no precipitate of cocaine with ammonia, and no benzoic acid with hydrochloric acid. It consisted of benzoyl-ecgonine (*Pharm. Jour.*, [3], xvi. 817). According to A. Bignon (*Pharm. Jour.*, [3], xvi. 721), the anæsthesia produced by a 5 per cent. solution of cocaine benzoate lasts during four consecutive hours, and is not preceded by the sensation of pain produced by the hydrochloride.

EXAMINATION OF COMMERCIAL COCAINE AND ITS SALTS.

The absolute purity of cocaine and cocaine salts intended for medicinal use is essential, as various undesirable and even dangerous symptoms are produced by certain impurities liable to be present.[1]

Crude Cocaine has for some time been manufactured in South America for export to European markets in place of coca leaves, which have been found liable to deterioration in transit. B. H. Paul (*Pharm. Jour.*, [3], xviii. 782) describes it as a white or yellowish pulverulent substance compressed into thin cakes. It contains not only earthy substances, sodium carbonate and lime salts, but also a waxy substance and traces of petroleum. Its manufacture has probably been effected by extracting the coca leaves with petroleum spirit, washing out the alkaloid with an acid, and then precipitating it with lime or sodium carbonate. It is represented as containing from 80 to upwards of 90 per cent. of alkaloid, but the proportion of crystallisable cocaine present varies considerably, in one instance not exceeding one-half of the total alkaloid present (85 per cent.). The remaining portion was precipitated on adding ammonia to its solution in hydrochloric acid in oily globules, which after a time collected at the bottom of the liquid as a viscid semi-transparent layer, which ultimately became more or less crystalline. In all cases the liquid remained quite

[1] The characters and tests for cocaine hydrochloride given in the *British Pharmacopœia* of 1885 are inadequate, and in several respects grossly inaccurate. In the first issue, it was incorrectly described as readily soluble in ether, whereas in fact it is practically, if not absolutely, *in*soluble. This mistake is corrected in the reprint, but the aqueous solution is still described as having a bitter taste, which is not a characteristic of the pure salt, and is said to yield a white precipitate with carbonate of ammonium, soluble in excess of the reagent, which is not the fact. "The aqueous solution dilates the pupil of the eye. It (? the aqueous solution) dissolves without colour in cold concentrated acids, but chars with hot sulphuric acid."

milky for a considerable time, in this respect presenting a marked contrast to the rapid clearing of the liquid, which takes place when pure cocaine is precipitated from the solution of its hydrochloride.

The analysis of a sample of crude cocaine by E. R. Squibb showed:—Moisture, 3·25 per cent.; residue insoluble in ether, 5·25; impurity soluble in ether, 0·50; pure alkaloid, 89·94; and loss, 1·06 per cent. (*Jour. Soc. Chem. Ind.*, viii. 724, 1013).

A convenient method of purifying cocaine is to recrystallise it several times from strong alcohol, and, when a certain degree of purity has been attained, precipitate the base from its solution in 10 parts of strong alcohol by addition of 5 measures of water.

Paul and Cownley have pointed out that the solubility of a sample of cocaine in petroleum spirit cannot be relied on as a proof of its purity, since cinnamyl-cocaine behaves similarly.

John Williams (*Year-Book Pharm.*, 1887, page 502) proposed to purify and assay commercial cocaine hydrochloride by dissolving it in the smallest possible quantity of absolute alcohol (sp. gr. 0·795), and adding to this solution six times its measure of dry ether, when the cocaine hydrochloride is precipitated in a finely-divided but perfectly crystalline condition. Unfortunately, as pointed out by B. H. Paul, the hydrochlorides of the amorphous bases and of benzoyl-ecgonine are precipitated under the same conditions; and hence the method is useless for the assay of crude cocaine hydrochloride or for the elimination of impurities, though serviceable for improving the appearance of a pure salt and converting it into a convenient form for use.[1]

Cocaine hydrochloride should be perfectly colourless, and soluble in water to a perfectly colourless solution, which ought to be absolutely neutral to litmus-paper. The solution of the pure salt keeps fairly well, but in presence of common impurities is decomposed with great facility. In the dry solid state, cocaine hydrochloride undergoes no change by keeping. It ought to be perfectly free from odour; but as sold it not unfrequently retains the odour of a solvent used in its preparation, or has a peculiar butyric or mousy smell, or even a distinct benzoic odour. In any case, a sample having a distinct odour must be regarded with suspicion.

Pure cocaine hydrochloride is always distinctly crystalline, though much of the commercial article presents an amorphous or granular

[1] Paul adds that it is a mistake to attempt the purification of cocaine hydrochloride at all. The free alkaloid is much more susceptible of purification, and may be obtained in very fine crystals either from ether or alcohol. From pure cocaine the hydrochloride can be readily prepared, as the neutral solution may be evaporated to dryness without decomposition, and the resultant dry salt can be readily converted into a good-looking crystalline condition by Williams' method.

appearance. The tendency to crystallise is so marked that B. H. Paul (*Pharm. Jour.*, [3], xviii. 781) regards an amorphous condition, or even difficult crystallisability, as an indication of the presence of impurity. Paul states that on dissolving 5 to 10 grains of a pure sample in 1 drachm of water and rapidly evaporating the solution (in a glass basin) on a water-bath, the dry residue obtained will be white and opaque, presenting a radiating crystalline structure, while in the case of an impure mixed salt the residue will be more or less yellow, translucent, and of a gummy or resinoid character.

The most definite test for the purity of cocaine hydrochloride is said by Antrich (*Ber.*, xx. 310) to be the optical activity. In dilute alcoholic solution, at 20° C., the specific rotatory power is $S_D = -(52^{\circ}{\cdot}18 + 0{\cdot}1588q)$, and $S_D = -(67{\cdot}982 - 0{\cdot}15827c)$; where q is the weight of dilute alcohol of ·9353 specific gravity at $\frac{20^{\circ}}{4^{\circ}}$ (which corresponds to a mixture of 6 parts by weight of absolute alcohol with 9 parts of water) in 100 parts by weight of the solution, and c is the weight of hydrochloride in 100 volumes of the solution. When $q = 0$, or, in other words, the solution is aqueous, $S_D = -52^{\circ}{\cdot}2$; when q is 100, $S_D = -68^{\circ}{\cdot}06$.

The characteristics of cocaine hydrochloride should be, according to Beekurts, that it should give a clear and colourless solution in water; leave no residue on ignition; give a colourless solution in concentrated sulphuric acid, when dissolved in the proportion of 0·020 gramme to 1 c.c.; that a concentrated aqueous solution should be absolutely neutral (to litmus); not immediately reduce potassium permanganate; and when heated with the latter reagent give off no odour of bitter-almond oil.

The *German Pharmacopœia* (1890) prescribes the following tests for cocaine hydrochloride:—0·1 gramme is dissolved in 5 c.c. of water, and 3 drops of diluted sulphuric acid added. This solution should be coloured violet by 1 drop of a 1 per cent. solution of potassium permanganate, and if kept in a closed vessel the coloration should but slightly decrease in half an hour. One c.c. of sulphuric or nitric acid should dissolve 0·1 gramme of a cocaine salt without coloration.

The following test is due to H. Maclagan (*Amer. Drug.*, 1887, page 22; *Pharm. Jour.*, [3], xvii. 686):—One grain of cocaine hydrochloride is dissolved in 2 ounces of water, 2 drops of strong ammonia are added, and the walls of the containing vessel rubbed from time to time with a glass rod; in a quarter of an hour a good crop of glistening crystals separate. When the cocaine is not very pure the solution remains clear, or else deposits only a small crop. With a good sample a dense precipitate is produced either at once or on stirring, and soon acquires a crystalline condition,

the liquid rapidly clearing. When the cocaine contains more than 4 per cent. of amorphous alkaloid the solution becomes milky.

B. H. Paul (*Pharm. Jour.*, [3], xviii. 783) has pointed out that the precipitate of cocaine produced in Maclagan's test redissolves if left for a long time in the ammoniacal solution, owing to its conversion into the soluble base benzoyl-ecgonine. He describes a quantitative application of the ammonia test (using a 2 per cent. solution of the salt) which, in the case of good samples free from odour and colour, will fairly indicate the purity and value; but, in the case of bad samples, regard must also be paid to the character of the precipitated alkaloid. This is done by adding the ammonia gradually, with constant stirring, as long as a crystalline precipitate forms and the liquid clears promptly. When the precipitate begins to form clots which adhere to the sides of the beaker, and the liquid remains milky, the precipitate already formed is separated, and the amorphous precipitate produced on further addition of ammonia collected separately.[1] The following results were obtained by B. H. Paul by the examination of commercial cocaine hydrochloride by the above process :—

Sample Number.	Water, per cent.	Ammonia Precipitate, per cent.	
		On Sample.	=On Dry Salt.
1	·90	85·6	86·3
2	·59	84·3	84·7
3	...	84·0	84
4	1·00	83·6	84·00
5	·43	82·6	82·95
6	1·19	81·35	82·33
7	·43	81·04	81·40
8	9·47	74·9	82·75
9	2·00	Cryst. 66·4 Amorph. 12·2	80·2
10	0·57	Cryst. 43·28 Amorph. 34·93	78·66
11	2·93	Cryst. 41·7 Amorph. 31·7	75·5
12	...	65·3	...

The ammonia precipitates from the first eight of these samples were perfectly crystalline, without any trace of stickiness; they deposited rapidly, and left the supernatant liquid quite clear and bright. In the case of samples 9, 10 and 11, a considerable proportion of the alkaloid was of an amorphous sticky nature, quite different from that obtained from a pure salt. No. 12 was so impure that it was impossible to effect a fractional precipitation quantitatively.

[1] The amorphous alkaloid when freed from colouring matter is a clear yellowish transparent substance, resembling thick canada-balsam, and the hydrochloride forms a varnish-like mass that cannot be reduced to powder.

Paul states that the principal impurity in the last four samples was undoubtedly the hydrochloride of the amorphous alkaloid associated with cocaine in coca leaves (see page 287), the salts having been probably produced by evaporating the solution of the mixed bases in hydrochloric acid; and it is questionable whether the presence of this amorphous base should be tolerated in a product which purports to be "*cocaine* hydrochloride."

Decomposition-Products of Cocaine.

BENZOYL-ECGONINE. $C_{16}H_{19}NO_4$; or $C_8H_{13}N(O.C_7H_5O).CO.OH$. This base may be prepared by the action of benzoic anhydride or benzoic chloride on ecgonine, and is also a product of the action of acids or water on cocaine. Hence it occurs as a bye-product of the manufacture of cocaine.[1] On a large scale, benzoyl-ecgonine is prepared by gradually adding a little more than one molecule of benzoic anhydride to a hot saturated aqueous solution of one molecule of ecgonine, and heating the mixture on the water-bath for about an hour. After cooling, the product is shaken with ether to remove unchanged benzoic anhydride and acid, and the residual benzoyl-ecgonine washed with a little water to dissolve unaltered ecgonine. The yield is about 80 per cent. of the ecgonine employed, and an additional quantity can be obtained by concentrating the mother-liquor and again treating it with benzoic anhydride.

Benzoyl-ecgonine crystallises with $4H_2O$ in transparent, flat, trimetric prisms, resembling ammonium oxalate, which melt at a variable temperature ranging from 87°–140°. When fusion occurs at the lower temperature (as happens when the heat is rapidly applied), the substance resolidifies on further heating, and melts again at 195°, turning brown at the same time.

Benzoyl-ecgonine is sparingly soluble in cold water, but readily in hot water, alcohol, and dilute alkalies and acids. It is almost insoluble in ether.

The *acetate* and *sulphate* of benzoyl-ecgonine crystallise in prisms. $BHAuCl_4$ forms small, yellow, anhydrous scales, soluble in alcohol but only sparingly so in water.

When heated with alkalies or with hydrochloric acid to 100° in sealed tubes, the base is decomposed into benzoic acid and ecgonine. By treatment with methyl iodide it yields cocaine.

[1] Benzoyl-ecgonine is easily produced by heating cocaine with about 20 parts of water in a closed tube. The cocaine melts at about 90°, but gradually dissolves on maintaining the temperature at 100°. The change is facilitated by agitation, and in about twelve hours a clear solution is obtained, which is only faintly acid if pure cocaine was employed.

Benzoyl-ecgonine does not appear to have much, if any, anæsthetic effect when applied to the eye, and exerts only a moderate dilating action on the pupil. R. Stockman states that it is very irritating to the mucous membranes, and when injected subcutaneously produces tetanic spasms. In many respects its action resembles that of caffeine, but paralysis of the sensory nerves is quite absent (*Pharm. Jour.*, [3], xvi. 898).

ECGONINE. $C_9H_{15}NO_3$; or $C_8H_{13}N(OH).COOH$. (See also page 270.) Ecgonine is obtained, together with benzoic acid and methyl alcohol, by heating cocaine with concentrated hydrochloric acid to 100° in sealed tubes (page 272).[1] Also, when cocaine or its hydrochloride is heated with 20 parts of water and 10 of baryta to 120° in sealed tubes, it is decomposed according to the equation :—

$$C_{17}H_{21}NO_4 + 2H_2O = C_7H_6O_2 + C_9H_{15}NO_3 + CH_4O.$$

The actual products are methyl alcohol, barium benzoate, and a compound of barium benzoate with the barium compound of ecgonine, $(2Ba(C_9H_{14}NO_3)_2 + Ba(OBz)_2 + xH_2O)$, which forms slender prismatic needles, very soluble in water and alcohol, but only slightly soluble in ether. This compound is a convenient source of ecgonine. On subjecting it to dry distillation it yields an isatropine, the chloroplatinate of which forms bulky, orange-red, deliquescent crystals containing $(C_8H_{15}NO)_2H_2PtCl_6$.

Ecgonine crystallises from absolute alcohol in monoclinic prisms containing 1 aqua, which melt at 198°; or, after drying at 140° to expel the water of crystallisation, at 205°. Ecgonine is very soluble in water, sparingly in absolute alcohol, and insoluble in ether. It has a slight bitter-sweet taste.

When ecgonine is heated with moderately strong sulphuric acid, neither carbonic oxide nor formic acid is formed, but a base is produced which bears the same relation to ecgonine that ether bears to alcohol. It unites both with acids and bases.

C. E. Merck (*Ber.*, xix. 3002) states that ecgonine, when distilled with nearly dry barium hydroxide, yields methylamine and not ethylamine as one of the products, thus agreeing with the behaviour of tropine when similarly treated.

When ecgonine (or anhydro-ecgonine) is oxidised with potassium permanganate, or nitric acid, succinic acid is formed (Ein-

[1] Liebermann and Giesel obtain ecgonine on a large scale by boiling the amorphous base obtained in the manufacture of cocaine for about an hour with hydrochloric acid. The filtered solution is evaporated to dryness, the residue treated with a little alcohol to remove impurities, and the residual ecgonine hydrochloride decomposed by sodium carbonate, the liberated base being recrystallised from alcohol.

horn, *Ber.*, xxi. 47), a fact which shows that the side-chain in the molecule of ecgonine must be either in the α- or β-position.

Ecgonine contains a carboxyl-group, and hence behaves at once as an acid and a base. It has a neutral reaction, but reacts with alkalies to form gummy compounds of faint alkaline reaction, which crystallise with difficulty and are very soluble in water and alcohol. *Ecgonine hydrochloride*, $C_9H_{15}NO_3,HCl$, forms triclinic tables, difficultly soluble in alcohol and melting at 246° C. $B_2H_2PtCl_6$, after drying at 140°, melts at 226°. It is extremely soluble in water, and is deposited in orange-red prisms on adding excess of alcohol to its aqueous solution. $BHAuCl_4$ is a greenish yellow, gummy substance, very soluble in water and alcohol.

With iodised potassium iodide, ecgonine yields a reddish brown precipitate, rapidly changing to reddish yellow, microscopic tables or prisms. In dilute solutions the precipitate is formed only after concentration. In the animal system, cocaine is converted into ecgonine, which may be detected in the urine by this test.

ANHYDRO-ECGONINE. $C_9H_{13}NO_2$; or $C_5NH_7Me.CH:CH.COOH$. This base is formed by the action of phosphorus oxychloride or pentachloride on ecgonine, or by heating cocaine for eight hours to 140° with glacial acetic acid which has been saturated with hydrochloric acid gas. It forms colourless crystals melting at 235°, soluble in water and alcohol, but insoluble in ether, chloroform, benzene and petroleum spirit.[1] When anhydro-ecgonine is heated with water to 150°, methylamine is liberated. It combines directly with bromine to form a base containing $C_9H_{13}Br_2NO_2$, the hydrochloride of which melts at 184°. The salts of anhydro-ecgonine are crystallisable. BHCl crystallises from absolute alcohol in white needles melting at 240°–241°.

Bases allied to Cocaine.

DEXTRO-COCAINE. $C_{17}H_{21}NO_4$. Einhorn and Marquardt (*Ber.*, xxiii. 469, 979) have found that by warming with aqueous potash for twenty-four hours, ecgonine is converted into a base which differs from ordinary ecgonine in being much less soluble in absolute alcohol, and having a much higher melting-point (254°); but especially in being dextro-rotatory.

From this dextro-ecgonine a synthetic dextro-cocaine may be prepared as a colourless oil, which solidifies on standing, and is readily soluble in ether, alcohol, benzene, and petroleum spirit.

Dextro-cocaine may be obtained in crystals, melting at 43°–45°,

[1] Hence it is best isolated by treating the solution of its hydrochloride with argentic oxide (compare page 20). It may be purified by precipitation from its alcoholic solution by ether.

by treating its solution with a crystal of benzoyl-dextroecgonine ethyl-ester.

The salts of dextro-cocaine crystallise well. BHCl is much more difficultly soluble than the hydrochloride of ordinary cocaine, and melts at 205° instead of 181°·5. $BHNO_3$ is especially characteristic. 100 parts of water at 20° C. dissolve 1·55 parts of the nitrate, which is precipitated in crystals on adding nitric acid to solutions of other salts of the base. This behaviour distinguishes dextro-cocaine from ordinary cocaine. $B_2H_2PtCl_6$ crystallises from hot water in yellowish needles. $BHAuCl_4$ crystallises from dilute alcohol in needles melting at 148°.

Dextro-cocaine was found to resemble ordinary cocaine in its physiological effects, except that local anæsthetic action commenced more rapidly, and disappeared in a shorter time.

With chromic acid, potassium permanganate, and auric chloride, dextro-cocaine behaves like cocaine.

COCETHYLINE, HOMOCOCAINE, or Benzoyl-ecgonine ethyl-ester, $C_{18}H_{23}NO_4$, is the higher homologue of cocaine, which base it closely resembles. It is prepared by heating benzoyl-ecgonine with ethyl iodide and alcohol for eight hours at 100°. It crystallises from alcohol in vitreous prisms melting at 108°–109°, and is also soluble in ether but nearly insoluble in water. The *chloroplatinate* forms bright yellow, rhombic plates, resembling the cocaine salt but more crystalline. Physiologically, homococaine is similar in its effects to cocaine, but is weaker and less toxic, and does not appear to be mydriatic.

The higher homologues of cocethyline, containing propyl and isobutyl groups, have been prepared by similar means; and also by passing hydrochloric acid gas into a solution of benzoyl-ecgonine in the corresponding alcohol.

CINNAMYL-COCAINE. $C_{19}H_{23}NO_4$; or $C_9H_{13}(CH_3)(C_9H_7O)NO_3$. This base has been obtained synthetically by passing dry hydrochloric gas into a solution of cinnamyl-ecgonine (prepared by heating ecgonine with cinnamic anhydride and water). It forms large colourless crystals melting at 121°, and is almost insoluble in water, but readily soluble in alcohol, ether, &c. When boiled with hydrochloric acid it is decomposed readily and quantitatively into cinnamic acid, ecgonine, and methyl alcohol. BHCl is precipitated as an oil which solidifies after a time on adding a large volume of ether to a strong acidulated solution of the salt in alcohol. $B_2H_2PtCl_6$ crystallises in microscopic needles melting at 217°. When treated with a cold solution of potassium permanganate cinnamyl-cocaine and its salts immediately evolve a strong odour of benzaldehyde (bitter-almond oil).

Cinnamyl-cocaine has been proved to occur naturally in coca leaves from various sources. Paul and Cownley (*Pharm. Jour.*, [3], xx. 165) examined a sample of leaves containing 1·75 per cent. of total alkaloid, nearly 0·5 per cent. being crystallisable from petroleum spirit, but which, nevertheless, contained very little real cocaine. On oxidation by permanganate the crystallisable alkaloid yielded abundance of benzaldehyde, and in other respects corresponded with cinnamyl-cocaine (methyl cinnamyl-ecgonine).

COCAMINE. *α*-Truxilline. $C_{38}H_{46}N_2O_8 + H_2O$. This base is contained in notable quantity in Truxillo coca leaves. Hesse found 0·6 per cent. in leaves of a different kind, and states that East Indian coca leaves, and especially those from Java, contain cocamine in considerable amount. Liebermann regards cocamine as identical with the base originally described by him as γ-isatropyl cocaine, and afterwards as α-truxilline; but Hesse contends that Liebermann's product was a mixture, of which cocamine was a leading constituent.[1]

Cocamine has a bitter taste. Hesse and Stockman found its physiological effect to be similar to that of cocaine, but somewhat weaker, and its anæsthetic action especially weak. On the other hand, G. Falkson alludes to γ-isatropylcocaine (cocamine) as a "deadly alkaloid," and Liebermann describes it as a heart-poison which does not produce anæsthesia. To its presence as an impurity, the occasionally highly toxic effects of commercial cocaine are not improbably due.

Cocamine is precipitated by caustic alkalies and ammonia from solutions of its salts, and after exposure at the ordinary temperature in a desiccator retains one molecule of water. It is readily soluble in alcohol, ether, benzene and chloroform, but differs from cocaine in being very sparingly soluble in petroleum spirit. Neither the free base nor its salts have been obtained crystallised. Repeated solution in hydrochloric acid and reprecipitation by soda was the process employed by Liebermann to purify the cocamine from the co-occurring isococamine (β-truxilline), which is also bitter, and produces numbness of the tongue very slowly by reason of its sparing solubility.

Both cocamine and its isomeride have been obtained synthetically. When hydrolysed by mineral acids they yield ecgonine, methyl alcohol, and cocaic and isococaic acids respectively.

Cocaic Acid, $C_9H_8O_2$, or $C_{18}H_{16}O_4$, called by Liebermann γ-isatropic acid or α-truxillic acid, is produced by boiling

[1] The composition of cocamine and its allies has formed the subject of an embittered controversy between Liebermann and Hesse (*Pharm. Jour.*, [3], xxi. 1109, 1129; xxii. 61, 101).

cocamine with hydrochloric acid. The isomeric *isococaic acid* (δ-isatropic or β-truxillic acid) is the similar product from isococamine. Cocaic acid melts at 274°, is tasteless and odourless, insoluble in water, and nearly insoluble in ether, from which, however, it crystallises in forms resembling benzoic acid. Isococaic (β-truxillic) acid melts at 206°. Both cocaic and isococaic acids yield cinnamic acid and other products on distillation.

Benzoyl-pseudotropine, $C_8H_{14}NO.C_7H_5O$, is a base isolated by Giesel from a narrow-leaved coca plant cultivated in Java (*Ber.*, xxiv. 2336). It somewhat resembles dextrococaine, but is optically inactive, and differs from other coca-bases in not yielding methyl alcohol on hydrolysis; for, when heated with hydrochloric acid under a reflux condenser for some hours, it is completely decomposed into benzoic acid and pseudotropine, $C_8H_{15}NO$ (see page 247). In this respect the base resembles atropine and the other tropeïnes.[1] Benzoyl-pseudotropine is obtained as a milky precipitate which does not become crystalline on adding sodium carbonate to the solution of one of its salts. The base may be extracted by ether, and on evaporating the solution is obtained as an oil which, when quite dry, solidifies in radiating crystals melting at 49° C. It has a strong alkaline reaction, and is easily soluble in alcohol, ether, chloroform, benzene and petroleum spirit. BHCl, obtained by passing hydrochloric acid gas into an ethereal solution of the base, crystallises in white needles melting at 271°. The solution gives a bulky crystalline precipitate with mercuric chloride. $B_2H_2PtCl_6$ is a flesh-coloured precipitate, insoluble in hot water, alcohol and ether. $BHAuCl_4$ crystallises from water in sparingly soluble yellow needles, melting at 208°. The *picrate* forms fine yellow needles, difficultly soluble in water. With potassium bichromate, benzoyl-pseudotropine yields a crystalline precipitate, instead of an oily one like cocaine and dextrococaine.

Amorphous Bases of Coca.

In isolating cocaine there is found in the mother-liquors a variable quantity of a basic substance commonly known as "amorphous cocaine," while the names cocaicine and cocainoïdine have also been applied to it. Amorphous cocaine is described by R. Stockman (*Pharm. Jour.*, [3], xvii. 861) as ranging in colour from dark yellow to dark brown, and consistence from that of treacle to a sticky tenacious solid, having a peculiar

[1] Liebreich finds that benzoyl-pseudotropine introduced into the eyes of rabbits occasions strong local anæsthesia and a slight enlargement of the pupil, in this respect acting more like cocaine than atropine.

smell resembling that of nicotine, and a bitter and aromatic taste. Stockman concludes that "amorphous cocaine" is in reality a solution of ordinary crystalline cocaine in hygrine, the liquid alkaloid said to have been found in coca leaves by Lassen. The amorphous alkaloid is extracted from the coca in greater or less amount by the processes now employed by manufacturers, and its presence is considered by Stockman to account for certain disagreeable effects resulting from the employment of cocaine containing the impurity. Thus if the hydrochloride of the impure alkaloid be used to produce anæsthesia of the conjunctiva considerable irritation ensues.

W. C. Howard (*Pharm. Jour.*, [3], xviii. 71) to a certain extent agrees with Stockman's view as to the nature of amorphous cocaine. He found that when the solution of the bases of coca in hydrochloric acid was completely precipitated with platinic chloride, and the liquid filtered after standing over-night, the mixed platinum salts obtained were amorphous or semi-crystalline, and somewhat light in colour. When the precipitate was washed with a large quantity of water at a temperature not exceeding 80° C., the cocaine chloroplatinate dissolved, and the alkaloid could be obtained therefrom in a crystalline state. The fraction of the platinum salt insoluble in water when decomposed by sulphuretted hydrogen, and extracted with ammonia and ether, left on evaporating the ether a liquid base which thickened considerably on keeping, but in which no crystals appeared even after a week. It had an intensely bitter taste, formed an uncrystallisable hydrochloride, and a chloroplatinate containing 18·5 per cent. of platinum (against 19·3 per cent. in the cocaine salt)[1] and not affected by hot water, all which characters distinguish the base from the description of hygrine given by Lossen (*Annal. der Pharm.*, cxxi. 374).

O. Hesse states that when working on the bases from the broad-leaved coca, separating the cocaine as hydrochlorate "by a special process," and ascertaining the absence of cocamine, the residual mixture was dissolved in dilute hydrochloric acid and the solution treated with ammonia in excess, this process of solution and reprecipitation being repeated until the precipitate dissolved in hydrochloric acid gave a solution which showed no fluorescence on dilution with water, thus proving its freedom from hygrine. The precipitate, after being further washed with water at 80° C., gave a melted mass which was spread on glass plates and dried at

[1] Hesse (*Pharm. Jour.*, [3], xviii. 71, 437) considers that Howard's platinum salt was hydrated, being in reality the chloroplatinate of an amorphous base isomeric with cocaine.

60°, by which means it was obtained in transparent, brittle, hygroscopic laminæ which were nearly insoluble in water and alkaline liquids, but dissolved readily in alcohol, ether, chloroform, benzene and petroleum spirit. The solution was alkaline to litmus, but without effect on phenolphthaleïn (*Pharm. Jour.*, [3], xviii. 71, 437). When boiled with alcoholic baryta, or heated in a sealed tube with hydrochloric acid, the amorphous base yields benzoic acid, and another product not yet identified.

From a later investigation (*ibid.*, xix. 867), Hesse concludes that the amorphous bases from true coca consist chiefly of benzoyl compounds of an oily non-volatile base, together with some cocamine; while, on the contrary, those obtained from Truxillo leaves consist essentially of cocamine, and the cinnamyl compounds of the before-mentioned oily base; and the cocamine is in each case accompanied by a base containing H_2 less than cocamine.

A specimen of the amorphous base from coca examined by B. H. Paul (*Pharm. Jour.*, xviii. 784) is described by him as being pale yellow, and of the consistence of thick Canada balsam. It had a faint odour at once suggestive of benzoïn and butyric acid, and a distinctly bitter taste, but produced no anæsthetic effect on the tongue until after the lapse of some minutes, and then very slight compared with that produced by cocaine.

HYGRINE. Under this name several bases have been described, which were either impure or actually dissimilar. The name was first applied by Lossen to a liquid volatile base which has not since been obtained. The hygrine of O. Hesse (*Pharm. Jour.*, [3], xviii. 438) is best prepared from the mother-liquor obtained in the preparation of "cocaidine" from amorphous cocaine. This is treated with caustic soda and ether, the ethereal solution separated and evaporated, and the residue distilled with water. The hygrine passes into the distillate, which is faintly acidified by hydrochloric acid, evaporated to dryness, and the residue treated with caustic soda and ether. The ether leaves on evaporation a brown oily residue, which, on treatment with dilute acetic acid, deposits a brown smeary mass, which is filtered off, the solution again treated with caustic soda and ether, and the ether evaporated.

Hygrine thus obtained is a yellowish oily substance having an odour suggestive of that of quinoline. It has a slight burning taste, and a strong alkaline reaction on litmus, but does not alter phenolphthaleïn. It is but little soluble in water or solution of caustic soda, but dissolves readily in alcohol, ether and chloroform. Hygrine volatilises with steam, and at a higher temperature may be distilled alone.

BHCl is crystallisable. Its dilute aqueous solution exhibits a marked fluorescence, not perceptible in a concentrated solution, and destroyed by sodium chloride and other substances. An aqueous solution of hygrine hydrochloride becomes milky on addition of caustic soda, owing to the separation of the free base in minute oily globules, which aggregate after a time. Hesse attributes to hygrine the formula $C_{12}H_{13}N$ and the constitution of a trimethylquinoline, but Liebermann regards it as a mixture of oxygenated bases, which may be separated by fractional distillation. The most volatile boils at 193°–195°, and has the formula $C_8H_{15}NO$, but is not identical with tropine (page 246). The less volatile portion of hygrine appears to contain $C_{14}H_{24}N_2O$, and cannot be distilled unchanged at the ordinary pressure. Neither of these bases is affected by heating to 120° with concentrated hydrochloric acid (*Ber.*, xxii. 675).

Hesse points out that hygrine probably does not pre-exist in coca leaves, but is a product of decomposition. He states that when sound coca leaves are moistened with ammonia, shaken with ether, and the ether treated with dilute hydrochloric acid, the acid liquid on dilution at first shows no fluorescence, but after a time exhibits this character distinctly.

R. Stockman (*Pharm. Jour.*, [3], xviii. 701) states that hygrine exists in coca leaves in very minute quantity only, and some manufacturers never meet with it. He found it in cocaine mother-liquors given him by Messrs Howard & Sons, and notably in the alcoholic tincture of *fresh* coca leaves. Stockman finds hygrine to distil very imperfectly with steam in presence of cocaine.[1] The whole of the statements respecting hygrine require confirmation.

Stockman describes hygrine as a brown oily liquid with a characteristic smell. A drop placed on the tongue causes a burning sensation. Frogs were killed by the subcutaneous injection of hygrine mixed with water. There was considerable irritation at the place of injection, while the muscles all over the body, the bowels, and the serous membranes were studded with numerous minute hæmorrhages.

Coca Leaves.

The coca leaves occurring in commerce are chiefly of two kinds,

[1] The treatment is stated to have decomposed the cocaine present, some benzoic acid passing over with the hygrine. It seems probable that a difficultly volatile or non-volatile benzoate of hygrine was formed. A better result would probably have been obtained by adding an alkali to the contents of the retort.

the one being obtained from *Erythroxylon coca*,[1] which was the original trade-product, and the other, which is of more recent importation, derived from Jamaica and St Lucia. Coca leaves contain, in addition to the ordinary plant-constituents and the characteristic alkaloids, cocatannic acid.

Cocatannic Acid (C. J. H. Warden, *Pharm. Jour.*, [3], xviii. 985) has the probable composition $C_{14}H_{18}O_8$. It forms a sulphur-yellow powder, which appears under the microscope in filiform crystals interlaced in masses. It melts at 189°–191° to a deep red liquid, and is only slightly soluble in cold water, cold absolute alcohol, ether and chloroform. In hot water it dissolves more readily, and rather freely in boiling absolute alcohol. A hot aqueous solution of cocatannic acid has an acid reaction. It yields no reaction with ferrous salts (according to some observers, green), but with ferric gives a dark green coloration, and reduces silver nitrate slowly in the cold and immediately on heating, but not Fehling's solution. It does not precipitate gelatin. The alcoholic solution gives, with alcoholic lead acetate, a precipitate varying from yellow to orange-red. When heated with hydrochloric acid to 100°, cocatannic acid yields a glucose and a phlobaphene. The products of potash-fusion do not appear to be characteristic. They are said to include butyric and traces of benzoic acid.

C. J. H. Warden (*Pharm. Jour.*, [3], xviii. 1010, 1027) has observed that coca leaves which are rich in cocatannic acid also contain much alkaloid, and suggests, with much probability, that the cocaine and allied alkaloids of coca leaves exist in combination with cocatannic acid. Warden, in nine specimens of the dry leaves from plants grown in different parts of India, found from 6·36 to 12·64 per cent. of *ash* (average 8·85 per cent.), and from 0·358 to 1·671 per cent. of "crude alkaloid" (average 0·982 per cent.). Warden did not succeed in obtaining a crystalline alkaloid from Indian coca, but does not consider the non-crystalline character detracts from its physiological activity (?).

A. G. Howard (*Pharm. Jour.*, [3], xix. 569) has published analyses of a large number of coca leaves from different sources. His results show that while *Erythroxylon coca* yields about ¾ per cent. of alkaloid, the proportion obtainable from most other species of *Erythroxylon* is extremely insignificant, and in some cases the alkaloid is wholly absent. In Brazil alone there are upwards of eighty species of *Erythroxylon*.

[1] The coca plant is a small shrub from 4 to 6 feet in height, growing and largely cultivated in Peru and Bolivia, and, to some extent, in Brazil and the Argentine Republic.

H. T. Pfeiffer (*Chem. Zeit.*, xi. 783, 818; *Jour. Soc. Chem. Ind.*, vi. 561) has described the following process of manufacturing crude cocaine hydrochloride direct from coca leaves:—The disintegrated leaves are digested in closed vessels at 70° C., for two hours, with a very weak solution of caustic soda and petroleum boiling between 200°–250°. The mass is filtered, pressed while still tepid, and the filtrate allowed to stand until the petroleum has completely separated from the aqueous liquid. The former is then drawn off and carefully neutralised with very weak hydrochloric acid, when a bulky, white precipitate of cocaine hydrochloride is obtained, together with an aqueous liquid from which a further quantity of the salt can be recovered by evaporation.

The dried product contains about 75 per cent. of real alkaloid, besides traces of "hygrine," gum, and other matters. A repetition of the process proved that the whole of the alkaloid was removed by a single treatment. The soda cannot be substituted by lime, nor the hydrochloric acid by other acid.

Assay of Coca Leaves. Pfeiffer employs a similar process for the *assay* of coca leaves, 100 grammes of which should be digested in a flask with 400 c.c. of water, 50 c.c. of 10 per cent. soda solution, and 250 c.c. of petroleum. The mixture is kept warm for some hours and shaken occasionally, then strained, the residue pressed, and the filtrate allowed to separate. The aqueous liquid is tapped off, and the oily layer titrated with $\frac{N}{100}$ hydrochloric acid. The number of c.c. required, multiplied by 0·042, gives the percentage of cocaine in the sample. The fresh leaves contain from 0·3 to 0·6 per cent., but this proportion decreases considerably if the leaves have been stored for any length of time before being worked up.

For the assay of coca, v. d. Marck (*Jour. Pharm.*, [5], xx. 500; *Analyst*, xiv. 115), after a trial of various processes, recommends that 50 grammes of the leaves should be mixed with 20 grammes of calcined magnesia and moistened with a little water, dried at 60°, and the mixture exhausted with ether. The ether is distilled off, and the residue treated with 30 c.c. of 2 per cent. hydrochloric acid. The solution is filtered, and repeatedly shaken with ether to remove colouring-matters. Ammonia is then added, and the cocaine extracted by shaking three times with 25 c.c. of ether. After standing for a short time over some fragments of calcium chloride, the ether is evaporated, and the residual alkaloid weighed.

For the estimation of the *cocaine* in coca leaves, A. B. Lyons (*Jour. Pharm.*, [5], xiii. 197) recommends that the finely-

powdered leaves should be macerated for twenty-four hours with eight times their weight of a mixture of 95 volumes of ether with 5 of ammonia. From an aliquot part of this liquid the alkaloid is extracted by agitation with acidulated water, the ether separated, and the alkaloid liberated from the aqueous liquid by means of ammonia and again extracted with ether, which is then evaporated to dryness and the cocaine weighed. The associated bases, being soluble in water and insoluble in ether, remain in the ammoniacal liquid. Lyons states that coca leaves do not contain more than 0·8 per cent. of cocaine, and sometimes the proportion is as low as 0·15 per cent. The leaves rapidly deteriorate in value, so that in six months they are practically worthless. The product from deteriorated leaves is always more or less coloured, and very little of it is crystallisable; while that from good leaves is almost colourless, and easily crystallises.

M. Bignon (Lima)[1] states that coca leaves dried in damp weather, with frequent turning, and sheltered from dew and moisture, yield easily 0·8 per cent. of alkaloid, and the finer sorts can give 1·0 per cent. and upwards under exceptional circumstances. Coca leaves dried in damp weather, or pressed into sacks before being completely dried, undergo a gradual ferment which ends in the complete destruction of the cocaine.

OPIUM ALKALOIDS.

Opium, the nature and characters of which are described at length on page 332, is remarkable for the large number of nitrogenised organic principles contained in it. At least nineteen alkaloids have been isolated from opium, and the list is probably still incomplete. Most of these bodies have well-defined basic properties, and the majority are poisonous. Some of them, as morphine and narcotine, occur in opium in considerable quantity, but the greater number are present in very small proportion, and are entirely absent from some samples.

The following table exhibits the leading characters of the nitrogenised principles which have been recognised in opium. In some cases the basic character is very feebly marked, while certain of the alkaloids (*e.g.*, pseudomorphine, oxynarcotine) are probably decomposition-products.

[1] *Pharm. Jour.*, [3], xvi. 267; xvii. 506. Bignon states that the Indian never chews coca leaves alone; but mixes them with ashes and lime, whereby the alkaloid is liberated, and thus obtains the anæsthetic properties and numbing effect upon the mucous membrane of the stomach which he desires.

List of Opium Bases.

Alkaloid.	Formula.	Discoverer.	Date.	Melting-Point, °C.	Optical Activity.	Basic Character.	Physiological Action.
Morphine,	$C_{17}H_{19}NO_3$	Serturner.	1816	...	L	Strong.	Powerful narcotic poison.
Codeine,	$C_{18}H_{21}NO_3$	Robiquet.	1832	155	L	Strong.	Narcotic poison.
Thebaine,	$C_{19}H_{21}NO_3$	Thiboumèry.	1835	193	L	Strong.	Violent tetanic poison
Papaverine,	$C_{20}H_{21}NO_4$	Merck.	1848	147	I	Very feeble.	Tetanising ; feebly narcotic.
Meconidine,	$C_{21}H_{23}NO_4$	Hesse.	1870	58	...	Strong.	... ...
Codamine,	$C_{20}H_{25}NO_4$	Hesse.	1872	121-126	...	Strong.	... ...
Laudanine,	$C_{20}H_{25}NO_4$	Hesse.	1870	166	L	Strong.	Active tetanic poison.
Laudanosine,	$C_{21}H_{27}NO_4$	Hesse.	1871	89	R	Strong.	Tetanic poison.
Lanthopine,	$C_{23}H_{25}NO_4$	Hesse.	1870	200	...	Very feeble.	Tasteless.
Protopine,	$C_{20}H_{19}NO_5$	Hesse.	1871	202	...	Strong.	Narcotic.
Cryptopine,	$C_{21}H_{23}NO_5$	T. and H. Smith.	1864	213	I	Strong	Hypnotic and mydriatic.
Rhœadine,	$C_{21}H_{21}NO_6$	Hesse.	1865	232	...	Well-marked.	Not poisonous.
Narcotine,	$C_{22}H_{23}NO_7$	Derosne.	1803	176	L	Very feeble.	Feebly poisonous.
Oxynarcotine,	$C_{22}H_{23}NO_8$	Brown (p. 329).	1875	...	...	Feeble.	... ...
Narceine,	$C_{23}H_{29}NO_9$	Pelletier.	1832	170	I	Feeble.	Purely hypnotic.
Pseudomorphine,	$C_{34}H_{36}N_2O_6$	Pelletier and Thiboumèry.	1835	Not fusible.	L	Very feeble.	Not poisonous.
Gnoscopine,	$C_{34}H_{36}N_2O_{11}$	T. and H. Smith.	1878	233	...	Weak.	... ...
Tritopine,	$C_{42}H_{54}N_2O_7$	Kauder.	1890	182	...	Diacid base.	... ...
Hydrocotarnine,	$C_{12}H_{15}NO_3$	Hesse.	1871	50	...	Well-marked.	Similar to narcotine.

In addition to the alkaloids in the above list, deuteropine, opionine, papaverosine, and porphyroxine (page 330) have been described, but their existence as individuals is very doubtful.

With one or two exceptions, the alkaloids of opium are strictly peculiar to *Papaver somniferum*; while, on the other hand, the poisonous alkaloid sanguinarine, which is present in all other papaveraceous plants, does not appear to exist in *Papaver*.[1] Indeed, with the exception of protopine, which is probably identical with the interesting alkaloid macleyine, $C_{20}H_{19}NO_5$, obtained by Eykman (*Year-Book Pharm.*, 1882, p. 33) from

[1] SANGUINARINE, $C_{17}H_{15}NO_4$, is best prepared from the root of *Sanguinaria Canadensis* (*Year-Book Pharm.*, 1871, 310; 1875, 256; 1879, 201). The root is exhausted with water acidulated with acetic acid, the solution precipitated by ammonia, the precipitate dried and exhausted with ether, and the ethereal solution treated with hydrochloric acid gas, which throws down the hydrochloride of sanguinarine ($BHCl + H_2O$) as a scarlet precipitate, which may be purified by solution in hot water and repetition of the treatment with ammonia, ether, &c. The free alkaloid melts at 160°, and crystallises from hot alcohol in small white needles having an acrid, burning taste. Sanguinarine is a powerful narcotic poison; the powder causes sneezing. It is insoluble in water, but soluble in ether, chloroform, amylic alcohol, benzene and petroleum spirit. The solutions exhibit a strong violet fluorescence without absorption-bands, and are optically inactive. The salts of sanguinarine are orange-red, and hence the free alkaloid is reddened by the fumes of hydrochloric acid. The precipitation of the bright red hydrochloride from the ethereal solution of the alkaloid, as above described, is a highly characteristic reaction. Alcoholic sulphuric acid behaves similarly. Aqueous solutions of sanguinarine salts exhibit a violet fluorescence, and are precipitated white by ammonia and bright red by potassio-iodide of mercury. $B_2H_2PtCl_6 + H_2O$ forms a bright orange precipitate, very slightly soluble in water.

CHELERYTHRINE, which occurs in chelidonium and several other plants, is regarded by Schiel as identical with sanguinarine, but E. Schmidt agrees with Naschold that the more probable formula is $C_{19}H_{17}NO_4$.

CHELIDONINE, $C_{20}H_{19}NO_5 + H_2O$, is the principal alkaloid of the twelve said to exist in the root of the common celandine (*Chelidonium majus*), and occurs in several other plants in association with sanguinarine or chelerythrine (or both). Chelidonine forms colourless monoclinic crystals melting at 130°, soluble in alcohol, but insoluble in water and but slightly soluble in ether. The salts of chelidonine are colourless, and have a very acrid and bitter taste. The *hydrochloride* forms fine crystals which require fully 300 parts of cold water for solution, which character may be used for isolating the alkaloid. Chelidonine is a tertiary base, and contains no methoxyl-group. With sugar and sulphuric acid it gives a violet coloration. (See E. Schmidt, *Pharm. Zeit.*, 1889, 58.)

Several other alkaloids besides those already named have been detected in *Chelidonium majus*, among them being α- and β-homochelidonine,

Macleya cordata (a poisonous Japanese plant), none of the nitrogenised substances found in opium appear to be identical with any of those extracted from other plants of the family.[1]

Constitution of Opium Bases.

Some of the opium bases are isomeric, while others are homologous, or else differ from each other by the increments C_2H_2, CO, H_2, HO, or multiples of these.

The tendency to combine with each other to form stable crystalline compounds, which renders the isolation and study of the cinchona bases so difficult (see Homoquinine), does not seem to exist in the case of the opium alkaloids.

The chemical constitution of the opium alkaloids is not yet thoroughly understood, but they have been proved to be derivatives of quinoline, and in some cases further advances have recently been made.

Morphine (compare page 167) has been proved by the researches of Wright, Grimaux, Hesse, Skraup, Knorr, and others to contain two hydroxyl-groups, one of which has a phenolic and the other an alcoholic function. The first of these can be readily replaced by alkyl and acid radicals, forming codeine, acetylmorphine, &c. The second hydroxyl-group may also be replaced,[2] with formation of bodies of the type of methocodeine,[3] which differs from thebaine by H_2, thus:—

Morphine, . .	$C_{17}H_{17}(OH)NO.OH$
Codeine, . .	$C_{17}H_{17}(OH)NO.OCH_3$
Methocodeine, . .	$C_{17}H_{17}(OCH_3)NO.OCH_3$ [3]
Thebaine, . .	$C_{17}H_{15}(OCH_3)NO.OCH_3$

$C_{19}H_{15}(OCH_3)_2NO_3$, and (probably) protopine (F. Selle, *Arch. Pharm.*, ccxxviii. 441). Stylophorine, the alkaloid of *Stylophoron diphyllum*, is apparently identical with chelidonine. Chelerythrine is stated to exist in the root of the yellow sea-poppy, *Glauceum luteum*, together with glaucine and glaucopicrine, both of which form crystallisable salts (Probst, *Annal d. Chemie*, xxxi. 241). Porphyroxine (a body distinct from Merck's alleged opium base) and puccine are said to exist in sanguinaria root; and two alkaloids have been found in *Eschscholtzia Californica*, one of which is probably methyl-chelidonine. The alleged presence of morphine has not been confirmed. Of all these bases, only sanguinarine and chelidonine have been fairly well studied; while the data respecting the others do not suffice to characterise them.

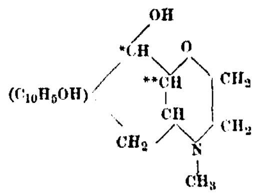
[1] A base identical with, or similar to, narcotine was isolated by T. and H. Smith from the fresh juice of the roots of *Aconitum Napellus*, but other observers have not confirmed this result.

[2] See footnote [1] on next page.

[3] It is not certain that methocodeine has the constitution ascribed to it in

The poisonous characters of morphine, which are both narcotic and tetanic, are shared qualitatively by derivatives in which only the hydrogen of the hydroxyl is replaced, as in codeine, ethyl-morphine, amyl-morphine, mono- and di-acetyl-morphine, benzoyl-morphine[1] and morphinyl-sulphonic acid. But when further substitution takes place, as in chlorocodeine and methocodeine (page 324), the product is not merely a nerve-poison, but a muscle-poison. Apomorphine, the constitution of which is probably not simply that of an anhydromorphine, is a muscle-poison analogous to methocodeine.[2]

L. Knorr (*Berichte*, xxii. 181, 1113) considers that morphine contains a reduced phenanthrene-nucleus and a methyl-group united with the nitrogen, and represents it by the following formula :—



It remains undecided whether the alcohol-hydroxyl is connected with carbon atom * or **.

Skraup and Wiegmann (*Monatsh.*, x. 110) have shown that this formula requires modification; for on heating morphine to a high temperature with alcoholic potash, a phenoloid body and ethyl-methylamine are formed, which fact proves that

the text. It is not improbable that the alcoholic hydroxyl remains intact, the second methyl-group being introduced into the body of the morphine molecule, thus :—$C_{17}H_{16}(CH_3)NO(OH).OCH_3$.

[1] By heating anhydrous morphine to 100°–110° with excess of benzoic chloride a dibenzoyl-derivative is obtained, and diacetylmorphine may be obtained in a similar manner. These compounds were first obtained by C. R. Alder Wright (*Jour. Chem. Soc.*, xxvii. 1631). When two acetyl-groups have been introduced into morphine no further substitution can be effected—a fact which confirms the view that the morphine molecule contains only two hydroxyl-groups (see Danckwortt, *Arch. Pharm.*, ccxxviii. 572).

[2] When treated with excess of acetyl chloride, apomorphine yields only a monoacetyl-derivative. Hence, probably, only one (the phenylic) hydroxyl atom exists in apomorphine, the second (alcoholic) having been eliminated during its formation from morphine.

in morphine both an ethyl and a methyl group are directly united to the nitrogen atom.

Pseudomorphine was formerly represented by the formula $C_{17}H_{19}NO_4$. Hesse found that the base contained a molecule of water which, when driven off, was recovered very rapidly. He therefore preferred the formula $C_{17}H_{17}NO_3$; but more recently has abandoned this for $C_{17}H_{18}NO_3$, or preferably $C_{34}H_{36}N_2O_6$, the base having the constitution of an oxydimorphine.[1] On the other hand, M. P. Cazeneuve (*Compt. Rend.*, 1891, p. 805) has obtained a violet colouring matter of definite composition by acting on morphine with paranitroso-dimethylaniline (page 75). This dye appears to be an indamine, analogous in constitution to Bindschedler's green; whereas, if pseudomorphine were derived from two molecules of morphine, the colouring matter would have contained two morphine residues, and had the constitution of a safranine (Part I. page 252). Combination is not effected by means of the hydroxyl-group having a phenolic function, since codeine yields a similar dye.

Narcotine, $C_{22}H_{23}NO_7$, contains three methyl-groups (besides that connected with the nitrogen), the first two of which may be successively removed by heating the alkaloid with strong hydrochloric acid, while by heating with fuming hydriodic acid the third group may be removed, nornarcotine, $C_{19}H_{17}NO_7$, being produced together with methyl iodide.

When narcotine is heated with water under pressure at 150°, it is split up in the first place with formation of opianic acid and hydrocotarnine (page 325):—

$$C_{22}H_{23}NO_7 + H_2O = C_{10}H_{10}O_5 + C_{12}N_{15}NO_3\,.$$

The two products subsequently react more or less completely to form meconin and cotarnine, thus:—

$$C_{10}H_{10}O_5 + C_{12}H_{15}NO_3 = C_{10}H_{10}O_4 + C_{12}H_{13}NO_3 + H_2O$$

(compare page 161).

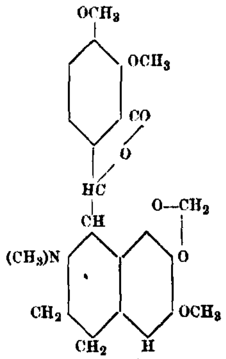
Opianic acid, $C_{10}H_{10}O_5$ (compare page 203), forms delicate white crystals. It is reduced to meconin (page 335) by nascent hydrogen, and by oxidation with dilute chromic acid mixture yields hemipinic acid, $C_{10}H_{10}O_6$. By the action of soda-lime, opianic acid yields methyl-vanillin, $C_9H_{10}O_3$, which when boiled

[1] On heating pseudomorphine with acetyl chloride, a tetracetyl-derivative is produced; a fact which indicates that the four hydroxyl-groups are still intact, and that the hydrogen atoms lost in the formation from morphine must have been united with carbon.

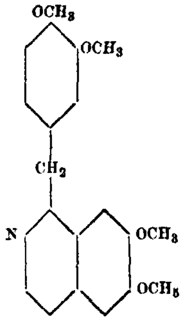
with hydrochloric acid gives vanillin, $C_8H_8O_3$ (Part I. page 62; see also Dott, *Pharm. Jour.*, [3], xiv. 641).[1]

Cotarnine, $C_{12}H_{15}NO_3$, is contained in the mother-liquor from which the meconin has crystallised. It forms a very soluble, yellow, bitter substance. It is a fairly strong base, soluble in ammonia and fusible in boiling water. When gently heated with very dilute nitric acid it yields methylamine nitrate and cotarnic acid, a bibasic acid containing $C_{11}H_{12}O_5$.

W. Roser (*Annalen*, ccliv. 334, 359), from a careful consideration of the evidence, considers narcotine to contain the residues of opianic acid and hydrocotarnine, and expresses it by the following graphic formula. It is closely related to *papaverine*, both being derivatives of a benzyl-isoquinoline.



Narcotine.



Papaverine.

W. Roser (*Annalen*, ccxlvii. 167) has obtained an isomer of narceine by treating narcotine methochloride in aqueous solution with caustic soda, when narcotine methyl-hydroxide is precipitated. On exposure to steam this changes into a base which is possibly identical with *narceine*, apparently in accordance with the equation :—$C_{22}H_{23}NO_7,CH_3OH + 3H_2O = C_{23}H_{29}NO_9,2H_2O$; or perhaps the new base is an anhydro-narceine containing $C_{23}H_{27}NO_8,3H_2O$.

Narceine has been expressed by the constitutional formula :—

$$(C_{13}H_{20}NO_4).CO.C_6H_2\begin{cases} CO.OH \\ O.CH_3 \\ O.CH_3 \end{cases}$$

[1] $C_6H_2\begin{cases} O.CH_3 \\ O.CH_3 \\ CO.OH \\ CO.OH \end{cases}$ Hemipinic acid. $C_6H_2\begin{cases} O.CH_3 \\ O.CH_3 \\ CO.H \\ CO.OH \end{cases}$ Opianic acid. $C_6H_2\begin{cases} O.CH_3 \\ O.CH_3 \\ CO.H \\ H \end{cases}$ Methyl-vanillin. $C_6H_2\begin{cases} O.CH_3 \\ O.CH_3 \\ \left.\begin{matrix} CO \\ CH_2 \end{matrix}\right\} O \end{cases}$ Meconin.

General Characters of Opium Bases.

Morphine, codeine, thebaine, papaverine, narcotine and narceine are the most important of the alkaloids of opium. The opium alkaloids form a group of which all the members exert a more or less narcotic and tetanising action, but in very varying degree. Thus morphine is almost purely narcotic and thebaine almost purely tetanising in its action.[1] Morphine, codeine and thebaine have strongly-marked basic characters. They are strongly alkaline to litmus, and afford stable salts.[2] Papaverine, narcotine and narceine, on the contrary, are very weak bases (compare page 305).

The free alkaloids of opium are generally but slightly soluble in water, but dissolve more readily in alcohol. In many instances the solutions of the free alkaloids are strongly alkaline to litmus. On the other hand, certain of them (*e.g.*, morphine, narceine, laudanine) exhibit a distinct phenoloid character, and form definite compounds with the alkalies. The different behaviour of the opium bases to solvents affords a valuable means of distinguishing and separating them. They are precipitated from concentrated solutions of their salts by caustic alkalies and alkaline carbonates, some of the precipitates dissolving in excess of the reagent. Most of the opium alkaloids (except papaverine and laudanosine) have a lævo-rotatory action on polarised light, but the specific rotatory power varies so greatly with the solvent and the concentration of the solution that the fact has a very limited practical value. Many of the opium alkaloids furnish characteristic colour-reactions when treated with strong acids and oxidising agents, which, with observations of their melting-points, crystalline form, and behaviour with solvents, will suffice for the recognition of most of them when in an unmixed state. Their separation is described on page 305 *et seq.*

Behaviour of Opium Bases with Solvents.

The following table shows the recorded behaviour of the opium bases with solvents. The figures are the number of parts of the solvent required for the solution of one part of the alkaloid. Apomorphine is not a natural constituent of opium, but is formed by the dehydration of morphine, and introduced into the table for convenience of comparison. The figures are the number of parts of the solvent required for the solution of 1 part of alkaloid.

[1] Thebaine appears to be the most poisonous of the leading alkaloids of opium. Papaverine appears to possess only very slight poisonous properties, if any.

[2] Codeine is distinctly more strongly basic than morphine, and a method of determining the former alkaloid has been based on the fact (page 323).

Alkaloid.	*Water.*		*Water with*		*Alcohol.*	*Amylic Alcohol.*	*Ether.*	*Chloroform.*	*Benzene.*	*Petroleum Spirit.*
	Cold. *	*Hot.*	*Caustic Soda.*	*Ammonia.*						
Morphine,	2300	460	Readily soluble.	Slightly soluble.	50 to 100, cold; 30, hot.	150, cold; 50, hot.	6100	Nearly insoluble.	Insoluble.	Insoluble.
Apomorphine,	Slightly soluble.	...	Soluble, turning black.	Soluble, quickly turning black.	Very soluble with green colour.	...	Very soluble.	Very soluble.	Soluble.	...
Pseudomorphine,	Insoluble.	...	Soluble.	Somewhat soluble.	Nearly insoluble.	...	Insoluble.	Insoluble.	Soluble.	...
Codeine,	75	17	Slightly soluble.	Same as with water.	Readily soluble.	7	Readily soluble.	Readily soluble.	12	Nearly insoluble.
Thebaine,	Insoluble.	...	Insoluble.	Sparingly.	10	60	140	18	19	Insoluble.
Papaverine,	Insoluble.	Very sparingly.	Insoluble.	Nearly insoluble.	45, cold; 4, hot.	70	250	Soluble.	36	Slightly, cold; readily, hot.
Meconidine,	...	...	Insoluble.	Sparingly.	Easily.	...	Easily.	Easily.	Easily.	...
Codamine,	...	Soluble.	Soluble.	Soluble.	Readily.	...	Soluble.	Soluble.	Soluble.	...
Laudanine,	...	...	Readily soluble.	...	Sparingly, cold.	...	647	Soluble.	Soluble.	...
Laudanosine,	Insoluble.	...	Insoluble.	Insoluble.	Readily.	...	19	Soluble.	Sparingly, cold; readily, hot.	...
Lanthopine,	...	...	Soluble.	Insoluble.	Sparingly.	...	Sparingly.	Readily.	Sparingly.	...
Protopine,	Insoluble.	...	Insoluble.	Soluble.	Sparingly.	...	Sparingly, soluble.	Soluble.	Nearly insoluble.	...
Cryptopine,	Nearly insoluble.	...	Soluble.	Slightly soluble.	Sparingly, hot.	...	Soluble, freshly ppted.	Soluble.	Slightly.	Insoluble
Rhœadine,	Nearly insoluble.	...	Insoluble.	Nearly insoluble.	Nearly insoluble.	...	1280	Nearly insoluble.	Nearly insoluble.	...
Narcotine,	25,000	7000	Insoluble.	Insoluble.	189, cold; 13, hot.	310	50, cold; 20, hot.	3	25	Nearly insoluble.
Oxynarcotine,	Insoluble.	Soluble.	Soluble.	Soluble.	Sparingly, hot.	...	Insoluble.	Insoluble.	Insoluble.	...
Narceine,	400	60	Soluble; insoluble in *strong NaHO*	Soluble.	300, cold; easily, hot.	Nearly insoluble.	Insoluble.	Nearly insoluble.	Insoluble.	Insoluble.
Tritopine,	...	...	Sol.; ppted. by large excess.	...	Soluble.	...	Sparingly.	Readily.	...	...
Gnoscopine,	Insoluble.	Insoluble.	Insoluble.	Insoluble.	1500	Insoluble.	Sparingly.	Soluble.	Sparingly.	Insoluble.
Hydrocotarnine,	...	...	Insoluble.	...	Readily.	...	Readily.	Readily.	Soluble.	...

Colour-Reactions of Opium Bases.

Alkaloid.	*Nitric Acid* (sp. gr. 1·42).	*Concentrated Sulphuric Acid.*			*Erdmann's Test* (page 146).	*Fröhde's Reagent* (page 147).	*Ferric Chloride.*
		Alone.	*On adding* $KClO_3$ or HNO_3.	*With Sugar.*			
Morphine,	Orange-red, turning yellow on heating.	Cold, no colour or faint pink; on heating, variable (page 314).	See page 314.	Purple, changing to deep red (p. 315).	...	Fine violet, turning blue or dirty green.	Greenish blue.
Apomorphine,	Blood-red, or reddish-violet.	No colour (or violet to brown).	...	No reaction.	...	Deep green, turning violet.	Rose-pink, changing to violet and black.
Pseudomorphine,	Orange-red, changing to yellow.	Cold, no colour, or olive green; on heating, dingy green (or purple), and finally red.	...	Olive, then dark green, changing to brown.	...	Violet, changing to blue and green.	Blue.
Codeine,	Yellow, not changing to red.	No colour; dirty brownish green on heating.	Blue on warming.	Cherry-red, changing to violet.[1]	Blue, on warming.	Dirty green, changing to blue and pale yellow (page 322).	No colour.
Thebaine,	Yellow.	Blood-red, turning orange yellow; olive-green on heating.	Same as with sulphuric acid alone	...	Orange-red.	Blood-red, turning orange-yellow and colourless.	No colour.
Papaverine,	Yellow.	Cold, little change; on strongly heating, violet-blue, afterwards fading slowly (characteristic).	No change.	...	Dull purple.	Green (changing to fine violet-blue), becoming blue and yellow.[1]	No colour.
Narcotine,	Red.	Darkens; changing to orange and brick-red on gently heating.	Carmine red.	Fine mahogany brown.	On warming, pink, changing to orange-red and violet.	Pink, changing to green, yellow, and orange.	No colour.
Narceine,	Yellow rapidly fading.	Brown, dissolving to yellow solution (changing to dark red).[1] If impure, red or blue colour.	No change.	Not characteristic.	Brown-yellow, becoming mahogany brown on heating.[1]	Brownish green, changing to yellow and reddish[1] (yellow-brown to blue).	...

[1] Great discrepancies occur in the descriptions of this reaction.

The solubility of opium bases, as of other substances, is much affected by the physical condition of the alkaloids, and to some extent by the manner of making the experiment.

Colour-Reactions of Opium Bases.

Several of the opium bases react in a more or less characteristic manner with potassium permanganate (see page 144).

Many of the opium alkaloids give brilliant, and in some cases characteristic, colour-reactions with mineral acids, with or without the aid of heat and the addition of oxidising agents. The colours obtained vary somewhat with the mode of applying the test and with the oxidiser employed. The colours obtained are modified in a marked manner by very slight traces of oxidising agents in the sulphuric acid used, and hence this reagent should be scrupulously free from iron and oxides of nitrogen. E. Kauder recommends that the purity of the sulphuric acid should be tested by codeine, which should give no colour even on heating, while in presence of the faintest trace of iron, such as may be taken up from long keeping in a bottle of common glass, a violet coloration is produced.

The colour-reactions of the opium alkaloids are best observed in the manner described in detail on page 313 *et seq.*

Many of the colour-reactions of the opium bases defy classification, and such of these as appear of value are described under the alkaloids to which they refer; but the table on page 302 shows many of the better-known reactions of the more important opium bases, according to the most reliable observers.

If a trace of narceine be evaporated with dilute sulphuric acid at 100° C. a beautiful violet-red coloration appears as soon as the liquid is sufficiently concentrated; changing to cherry-red by continued heating. After cooling, the addition of a trace of nitric acid or a nitrite produces bluish violet streaks in the red liquid. The test, which is due to Plugge (*Jour. Chem. Soc.*, lii. 870), is said to be very delicate and characteristic. With traces of morphine, codeine, or papaverine the liquid remains quite colourless; with larger quantities of either of the two former bases a faint rose-red tint is obtained, with thebaine a greenish yellow to brown colour, and with narcotine a red to reddish brown.

According to Serena (*Analyst*, x. 149), the following colour-reactions are produced on treating certain of the opium alkaloids *successively* with a few drops of concentrated sulphuric acid and a very small quantity of a dilute solution of ferric chloride, with the aid of slight heat.

Alkaloid.	*With Sulphuric Acid.*	*On adding Ferric Chloride.*
Apomorphine, .	Not changed.	Violet streaks at point of contact, the bluish green mass becoming light violet on heating.
Codeine, . . .	Light violet-red, deepened by heat (compare p. 322).	Sky-blue.
Papaverine, . .	Purplish red.	Colourless; on heating, violet.
Opionine, . . .	No coloration.	Green; rapidly becoming deep-blue.
Narceine, . . .	Coffee-brown.	Bluish green.
Codamine, . .	... ...	Green-blue; at 100°, violet.

The following table shows the colour-reactions observed by Hesse (*Jour. Chem. Soc.*, xxiv. 1064) when certain of the opium bases are treated with pure concentrated sulphuric acid, and with acid containing traces of oxide of iron or oxides of nitrogen. The reactions with ferric chloride are also shown.

Alkaloid.	With *pure Sulphuric Acid.*		With *Acid containing Oxide of Iron.*		With *Ferric Chloride.*
	At 20° C.	At 150° C.	At 20° C.	At 150° C.	
Codeine, .	Colourless.	Dirty green.[1]	Blue.	Dirty green.	No reaction.
Codamine, .	Colourless.	Dirty red-violet.	Intense green-blue.	Deep violet.	Dark green.
Lanthopine,	Colourless.	Brownish yellow.	..	..	No reactions.
Laudanine, .	Very faint rose-red.	Deep red-violet.	Intense rose colour.	Green, changing to deep violet.	Emerald-green
Laudanosine,	Faint rose-red.	Deep red-violet.	Brownish-red (resembling cobalt nitrate solution).	Green, changing to deep violet.	No reaction.
Protopine, .	Yellow, changing to red and bluish red.	Dirty greenish brown.	Deep violet.	Dirty greenish brown.	No reaction.
Cryptopine,	Yellow, changing to violet.[2]	Dirty green.	Deep violet.	Dirty green.	No reaction.
Hydrocotarnine, .	Yellow.	Crimson-red, changing to dirty red-violet.	..	Dirty red-violet.	..

[1] According to E. Kauder (*Pharm. Jour.*, [3], xviii. 250), if the sulphuric acid be quite pure no coloration is yielded with codeine even on heating, but a blue colour is produced if traces of iron be present. Cryptopine dissolves with violet colour, changing to deep blue, and fading to greenish on standing or heating to 150°. In presence of oxide of iron, cryptopine is said to dissolve in sulphuric acid with deep violet-rose colour, changing to violet and deep blue, and becoming greenish on heating to 150°. The hydrochloride gives a yellow coloration when first treated with acid.

[2] According to Merck, laudanine gives a violet colour with ferric chloride.

Hesse employs the colour-reactions of the opium bases with pure sulphuric acid as a means of grouping them, thus :—

Coloration at 150°.	*Alkaloids.*
Dirty dark green.	Codeine, morphine, pseudomorphine.
Dirty red-violet.	Codamine, laudanine, laudanosine, narcotine, hydrocotarnine.
Dirty green to green-brown.	Thebaine, cryptopine, protopine.
Dark violet or blue.	Papaverine.[1]
Black-brown to dark brown.	Narceine, lanthopine.

With acid containing iron, codamine, laudanine and laudanosine are stated to give a dark violet colour, while narcotine and hydrocotarnine react in the same way as with pure acid.

It will be seen that several of the reactions described by Hesse differ in a marked manner from those recorded by other observers. As in the case of other colour-observations, the only safe way is to compare the substance under examination side by side with products of known purity.

Lafon's reagent, prepared by dissolving 1 gramme of ammonium selenite in 20 c.c. of strong sulphuric acid, is stated by da Silva (*Compt. Rend.*, cxii. 1266) to give the following colour-reactions with the opium bases:—*Codeine*, magnificent green coloration; *morphine*, greenish blue, changing to chestnut brown; *narcotine*, blue, turning violet and then reddish, with slight reddish precipitate after long standing; *narceine*, yellowish green, changed to brown and red, with red precipitate on standing; *papaverine*, blue, passing to dull green, violet and red, with a slight bluish precipitate on standing.

Determination and Separation of Opium Bases.

Morphine, codeine, and thebaine may be titrated with ease and accuracy by a standard mineral acid, using litmus or methyl-orange as an indicator (page 130). On the contrary, they have little or no action on phenolphthaleïn, the reaction with which, however, is not sharp in the case of morphine (page 311).

Papaverine, narcotine and narceine, on the contrary, do not affect litmus, and their salts may be titrated with litmus and stan-

[1] Hesse states that, when absolutely pure, papaverine dissolves in small quantities of sulphuric acid without coloration; but, generally, on warming a crystal of papaverine with concentrated sulphuric acid, a dark blue colour is produced. Dott also obtains no coloration in the cold, and the blue colour on strongly heating only. A red coloration before heating is generally due to thebaine.

dard alkali, just as if the acid were uncombined (Plugge, *Pharm. Jour.*, [3], xx. 401); and the first two of them being alkaloids also evince their feeble basic characters by the fact that they are extracted by chloroform from acid solutions. Their salts, especially with certain organic acids (*e.g.*, acetic, benzoic), are very unstable, many of them being decomposed slowly by cold and rapidly by hot water. Hence, when a compound of the alkaloid with a mineral acid is treated with a neutral solution of acetate of sodium, or even with a slightly acid solution, the free alkaloid is precipitated.[1] A faintly acid solution of sodium acetate will indicate 1 part in 40,000 of narcotine, 1 in 30,000 of papaverine, and 1 in 600 of narceine, none of the other opium bases being precipitated.

On the foregoing and similar facts, P. C. Plugge (*Analyst*, xii. 197) has based the following process of separating the leading alkaloids of opium. The aqueous solution of the hydrochlorides is mixed with a concentrated solution of sodium acetate, and filtered after twenty-four hours. The precipitate, consisting of pure narcotine and papaverine, is washed with a little water, and dissolved in a minimum of dilute hydrochloric acid. The liquid is diluted till it contains not more than $\frac{1}{400}$ of narcotine, when potassium ferricyanide is added. This precipitates papaverine very perfectly. After standing twenty-four hours the liquid is filtered, and the precipitate of *papaverine* hydroferricyanide either weighed as such, or washed with a little water, decomposed by dilute caustic soda, and the liberated alkaloid dissolved in dilute acid and reprecipitated with ammonia. In the filtrate from the precipitate produced by the ferricyanide the *narcotine* is precipitated by ammonia. The filtrate from the precipitate produced by sodium acetate is concentrated to a small volume at 100°, cooled thoroughly, and filtered after twenty-four hours. The deposited *narceine* is filtered off, and washed with a little water. The filtrate is mixed with a strong solution of sodium salicylate, and the crystalline precipitate of *thebaine* salicylate separated after twenty-four hours, and washed with a little water, dried at 100°, and weighed. On subsequent treatment on the filter with dilute soda or ammonia, till the washings are free from salicylic acid (as indicated by evaporating to dryness, and the non-production of a violet coloration on moistening the residue with

[1] This observation is due to P. C. Plugge (*Arch. Pharm.*, [3], xxiv. 994; *Analyst*, xii. 197). The reaction not only distinguishes papaverine, narcotine and narceine from morphine, codeine, and thebaine, but also from caffeine, cocaine, conine, atropine, pilocarpine, strychnine, brucine, quinine, cinchonine and cinchonidine. The cinchona bases are precipitated if the sodium acetate is at all alkaline.

ferric chloride), pure *thebaine* is left. The filtrate from the thebaine salicylate is acidulated with hydrochloric acid, the precipitated salicylic acid filtered off, and the filtrate repeatedly shaken with chloroform. This dissolves the remaining salicylic acid, and traces of narceine and thebaine, which may be recovered by evaporating the chloroform. The acid liquid separated therefrom is concentrated somewhat, made exactly neutral to litmus, and mixed with potassium thiocyanate (sulphocyanide), which throws down the *codeine* as an acid thiocyanate. Twenty-four hours should be allowed for its complete separation.[1] The filtrate should be treated with a slight excess of ammonia, and time allowed for the separated morphine to become crystalline. The liquid is then shaken with chloroform or ether to remove the remainder of the codeine and traces of other bases. After separation it is acidulated to dissolve the morphine, heated to 60° C., and the morphine shaken out with hot amylic alcohol, after addition of a slight excess of ammonia or carbonate of sodium. Plugge's results, obtained in test experiments, except in the separation of codeine and morphine, were very satisfactory, considering the difficult nature of the problem to be solved.[1] But the methods are not to be regarded as having the same quantitative accuracy as those for the separation of the metals.

Another method of separating the principal alkaloids of opium consists in treating the solution with an alkaline carbonate or ammonia, and agitating with benzene, when morphine and narceine are left insoluble, the remainder passing into the benzene. Much the same separation occurs with chloroform, except that pseudomorphine is left with the insoluble alkaloids.

D. B. Dott has communicated to the author the following method of separating the chief bases of opium :—Treat the solution of their mixed hydrochlorides with a 10 per cent. solution of caustic soda, and wash the precipitate, which will consist of narcotine, papaverine and thebaine, the alkaline solution containing morphine, codeine and narceine. On agitating the filtrate with chloroform, the *codeine* will be extracted; and on separating the alkaline liquid, acidulating it, and rendering it faintly alkaline with ammonia, the *morphine* will be precipitated, the *narceine*, from its greater solubility, remaining dissolved. It can be recovered by

[1] The separation of codeine and morphine by this process is very imperfect. If the solution be too strong, morphine is precipitated with the codeine, and if this condition be avoided the precipitation of the codeine is incomplete. In test-experiments Plugge only recovered 70 per cent. of the codeine used. Hence it is better to omit the precipitation with thiocyanate altogether, precipitate the morphine with ammonia, and extract the codeine from the filtrate by ether or chloroform, after adding caustic soda (compare page 323).

evaporating the liquid to dryness and treating the residue with strong alcohol. From the bases precipitated by caustic soda, the *thebaine* can be separated fairly well by crystallisation as acid tartrate.

Narcotine and papaverine may also be separated from thebaine (and codeine) by dissolving the free bases in dilute alcohol, rendering the liquid faintly acid with acetic acid, and adding three volumes of boiling water, when the narcotine and papaverine are precipitated; or sodium acetate may be used as already described. Narcotine and papaverine may likewise be separated by solution in boiling water containing one-third part of oxalic acid, when an acid papaverine oxalate crystallises out on cooling. The process should be repeated several times, and the narcotine finally precipitated by ammonia and crystallised from boiling alcohol.

The following is an epitome of Hesse's method of separating the rarer opium bases from the mother-liquors left from the preparation of morphine by the Robertson-Gregory process.[1] The aqueous extract of opium is first precipitated by calcium chloride, the filtrate from the calcium meconate concentrated, and the hydrochlorides of morphine, pseudomorphine and codeine separated by crystallisation. The mother-liquor is diluted with an equal bulk of boiling water, excess of ammonia added, the precipitate removed by filtration and dissolved in acetic acid. The filtrate is agitated with ether, the ethereal layer shaken with excess of acetic acid, and the acetic solution mixed with that of the ammonia precipitate. The acetic acid solution is then treated with excess of caustic soda, which precipitates papaverine, narcotine, thebaine, some cryptopine, protopine, laudanosine and hydrocotarnine; while lanthopine, laudanine, codamine, meconidine, and a portion of the cryptopine remain in solution. The alkaline liquid is neutralised, ammonia added, the bases again extracted by ether, and shaken out with acetic acid. The acetic acid is neutralised with ammonia, when a little lanthopine separates out in twenty-four hours, and the filtrate is treated with more ammonia. The precipitate formed is dissolved in a very small quantity of boiling dilute alcohol, which on cooling deposits white crystals of mixed *laudanine* and *cryptopine*. On evaporating the alcoholic solution,[2] and treatment of the residue with ether, a solution is obtained from which *codamine* may be isolated, either by addition of fused

[1] For E. Kauder's modification of Hesse's method, see *Arch. Pharm.*, ccxxviii. 419; and *Jour. Chem. Soc.*, lx. 227.

[2] Hesse could obtain no meconidine from this solution, and hence concludes that it had been decomposed by the preceding operations, as he had previously obtained it from a similar source by another process (*Ann. Chem. Pharm.*, cliii. 47; Watts' *Dict. Chem.*, vi. 883).

calcium chloride (which causes water, colouring-matter, and crystals of codamine to separate), or by conversion into the acetate, and this into the hydriodide.

The mixture of bases insoluble in caustic soda is digested with dilute alcohol, and acetic acid added till the liquid is faintly acid to litmus. On adding three measures of boiling water, a crystalline precipitate of *papaverine* and *narcotine* is thrown down. The filtrate, freed from alcohol by evaporation, on adding strong hydrochloric acid, will give a precipitate of cryptopine hydrochloride; but in order to avoid the conversion of thebaine into its non-crystalline isomer thebaïcine, it is preferable to add tartaric acid, which throws down crystalline *thebaine* acid tartrate. The mother-liquor of this is neutralised with ammonia, and mixed with 3 per cent. of its weight of sodium bicarbonate made into a paste with water. After standing about a week, a black, pitchy mass separates, the filtrate from which gives with ammonia a precipitate which is treated with boiling benzene, the filtrate being also extracted by agitation with benzene. On shaking the united benzene solution with a saturated aqueous solution of sodium bicarbonate, *laudanosine* crystallises out; and the benzene filtered from this yields *hydrocotarnine* hydrochloride on passing hydrochloric acid gas. The portion of the ammonia precipitate left undissolved by benzene contains cryptopine and protopine. These bases are converted in hydrochlorides, and the solution treated with strong hydrochloric acid, when the *protopine* hydrochloride forms a horny deposit which adheres to the sides of the glass, and is easily freed from the gelatinous *cryptopine* salt by washing with a little water.

Narceine is mentioned as existing in the liquors, but the stage at which it is separated is not stated.

Morphine. Morphia.

$C_{17}H_{19}NO_3$; $C_{17}H_{17}NO(OH)_2$; or $C_{17}H_{17}(OH)NO.OH$.

Morphine is the most important of the bases contained in *opium*, in which it exists in combination with sulphuric and meconic acids.

The mode of preparing morphine may be gathered from the methods of assaying opium (see also last page).

Morphine crystallises in transparent, colourless, trimetric prisms, which are usually very short. They contain one molecule of water,[1] which is given off slowly at a temperature of 90° and more rapidly at 100° C. (*Pharm. Jour.*, [3], xviii. 701, 801; xix. 61, 148, 180). At or above 200° morphine partially volatilises, melts, and turns brown, becoming carbonised at a somewhat higher temperature.

[1] D. B. Dott found the proportion of water lost to correspond more nearly to $8C_{17}H_{19}NO_3+9H_2O$.

Morphine is inodorous, has a persistent bitter taste, and is a powerful narcotic poison.

Morphine is nearly insoluble in cold water, requiring, according to Chastaing, 33,333 parts at 3° and 4545 at 22°.[1] At 42°, the solubility is 1 in 2380, and in boiling water about 1 in 460 (*Year-Book Pharm.*, 1882, p. 30). The solution has an alkaline reaction. Morphine dissolves in 30 parts of boiling or 50 of cold absolute alcohol, and in a somewhat smaller quantity of rectified spirit. In ether and chloroform it is almost insoluble when in a crystallised state, but dissolves sparingly when freshly-precipitated and amorphous. A useful solvent for morphia is a mixture of equal volumes of ether and acetic ether (ethyl acetate); but even in this its solubility is limited, especially in the crystalline state. Amylic alcohol dissolves morphine sparingly (1 : 150) in the cold, but when heated is a fairly good solvent for it (1 : 50). The alkaloid dissolves best when liberated from one of its salts in presence of amylic alcohol.

In benzene and petroleum spirit, morphine is practically insoluble, as also in volatile oils.

According to Florio (*Gaz. Chim. Italiano*, xiii. 496) 100 parts of the following solvents dissolve of morphine :—

Solvent.	Morphine dissolved by 100 of Solvent.		
	At 10°-11° C.	At 56° C.	At 78° C.
Alcohol, absolute,	1·132	...	8·623
,, 90 per cent.,	0·377	...	2·991
,, 75 per cent.,	0·223	...	1·985
Wood-spirit,	1·675	8·466	...
Fusel-oil,	0·268	...	2·247
Benzene,	0·020	1·285	...
Chloroform,	0·040	...	...
Ether, absolute,	0·023	...	...

A. B. Prescott (*Jour. Chem. Soc.*, xxix. 405) has pointed out the great influence the physical condition of morphine has upon its relation to solvents, and has determined the proportion of different solvents requisite for the solution of morphine in the crystalline, amorphous, and "nascent" conditions; by the last term meaning that in which the alkaloid exists when liberated by ammonia or an alkaline carbonate from the aqueous solution of one of its salts. The following are Prescott's figures :—

[1] Dott gives the solubility of morphine in water at 15° C. as 1 in 2500.

Condition of the Morphine.	Parts of Solvent required.			
	Ether.	*Chloroform.*	*Amylic Alcohol.*	*Benzene.*
Crystallised, . . .	6148	4379	91	8930
Amorphous powder, . .	2112	1977	...	...
"Nascent" state, . .	1062	861	91	1997

Other figures for the solubility of morphine are given on page 301.

Solutions of caustic potash and soda dissolve morphia readily, as also do baryta and lime water, and, to a limited extent, ammonia also. Solutions of caustic alkalies dissolve quantities of morphine equivalent to the bases contained in them, with the formation of unstable morphinates which are decomposed by carbonic acid and assume a dark brown colour on exposure to air. Crystalline morphinates of potassium, barium, and calcium have been obtained. From these facts, and the blue reaction with ferric chloride, Chastaing (*Jour. Pharm.*, [5], iv. 19) inferred that morphine possessed a phenoloid character, and this view has been fully borne out by the later researches of Grimaux and Hesse (page 296).

Solutions of morphine are lævo-rotatory. In alcoholic or dilute acid solution, S_a is said to be $-89°·8$ and $S_D - 70°$. For the hydrochloride, the value is $S_D = -100°·67 - 1°·14$ C. In alkaline solution, the value of S_a for morphine is stated to be $-45°·2$.

Morphine is very sensitive to the action of oxidising agents, a fact which is often used for its detection (page 314 *et seq.*). It reduces salts of gold and silver, permanganates, ferricyanides, iodic and periodic acids, &c. The reactions of morphine with strong sulphuric and nitric acids are described on pages 313, 314.

When morphine is heated with strong hydrochloric acid or zinc chloride it loses the elements of water and is converted into apomorphine, $C_{17}H_{17}NO_2$ (page 319).

SALTS OF MORPHINE.

Morphine dissolves readily in dilute acids, forming salts which are perfectly neutral in reaction to litmus and methyl-orange, and hence it may be titrated with accuracy by the aid of standard hydrochloric acid and either of these indicators. With phenolphthaleïn morphine does not give a sharp reaction, but the point of neutrality is approximately the same as if the acid of the morphine salt were in a free state.

The salts of morphine are mostly crystallisable, and are all bitter and very poisonous. They are generally soluble in water and in

alcohol, but are insoluble or only slightly soluble in amylic alcohol, ether, chloroform, benzene, or petroleum spirit. Morphine is not removed from its acid or neutral solutions by agitation with any of the above solvents, except imperfectly by amylic alcohol.

The following table shows the formulæ of the more important salts of morphine, the percentage of morphine hydrate, the relative dose, and D. B. Dott's figures for their solubility in cold water (*Pharm. Jour.*, [3], xiii. 404; xvi. 653):—

Morphine Salt.	*Formula.*	*Morphine Hydrate, per cent.*	*Relative Dose.*	*Solubility in Water at 15°·5 C.*
Hydrochloride, .	$BHCl + 3H_2O$	80·69	1·00	1 part in 24.
Sulphate, . .	$B_2,H_2SO_4 + 5H_2O$	79·94	1·00	,, 23.
Acetate, . .	$B,C_2H_4O_2 + 3H_2O$	75·98	1·04	,, 2½.
Lactate, . . .	$B,C_3H_6O_3$	80·80	1·00	,, 8.
Tartrate, . .	$B_2,C_4H_6O_6 + 3H_2O$	78·29	1·02	,, 9¾.
Meconate, . .	$B_2,C_7H_4O_7 + 5H_2O$	70·46	1·14	,, 34.

Morphine Hydrochloride, or Morphia Hydrochlorate, $BHCl + 3H_2O$, crystallises in colourless silky fibres, soluble in half its weight of boiling water and in 40 parts of cold rectified spirit. It becomes anhydrous at 100° C. The commercial salt often has a buff or brownish tint from admixture of resinous matters, which are detected by the brown or black colour assumed by the salt when heated to 130° C.

Morphine Hydriodide, $BHI + 3H_2O$, is obtained as a compact mass of hair-like needles on mixing a concentrated alcoholic solution of potassium iodide with a concentrated solution of morphine hydrochloride. The product only slowly redissolves on adding more spirit, and is very sparingly soluble in water, especially in presence of potassium iodide. The *hydrobromide* can be obtained similarly.

Morphine Sulphate, $B_2H_2SO_4 + 5H_2O$, closely resembles the hydrochloride. It loses $3H_2O$ at 100°, and the remaining two atoms at 110°. It exists naturally in opium.

Morphine Acetate (see above) is a white, or faintly yellowish white, obscurely crystalline powder. It is readily soluble and crystallisable. It is partially decomposed by boiling or evaporating its aqueous solution, crystals of morphine being deposited.

Morphine Tartrate, $B_2C_4H_6O_6 + 3H_2O$, is readily soluble, but the *acid tartrate*, $BC_4H_6O_6$, only sparingly so. Their solutions are not precipitated by caustic alkalies, alkaline carbonates, or chloride

of calcium. The tartrate is best detected by precipitating the concentrated solution with potassium acetate and acetic acid in presence of alcohol (Vol. I. page 457). After boiling off the alcohol, the morphia can be precipitated from the filtrate by an alkaline carbonate or ammonia.

Morphine Meconate (see above) is interesting as being the form in which morphia largely exists in opium. When morphine and meconic acid are dissolved in absolute alcohol, and the solution is evaporated, an amorphous, hygroscopic, very soluble residue is obtained, which in concentrated solution deposits crystals of neutral morphine meconate containing 5 aqua, even in presence of sufficient meconic acid to form the acid salt.

DETECTION AND DETERMINATION OF MORPHINE.

Free morphine, when pure or in the form of one of its ordinary salts, is readily detected. Its determination is easy when unmixed with interfering substances, but as it exists in opium is attended with considerable difficulties. Most of the colour-reactions of morphia are best observed by operating on the solid substance, but for certain qualitative tests and for all quantitative methods the alkaloid must be in solution.

A. *Reactions of Solid Morphine.* For observing these reactions a minute fragment or crystal of the solid alkaloid or its salt should be employed, and the experiment should be conducted in a small porcelain basin or crucible. The residue obtained by the evaporation of the solution of morphine in alcohol or amylic alcohol is well-suited for the operation.

1. Solid morphine treated with a drop of a *perfectly neutral* solution of ferric chloride or iron-alum gives a very characteristic deep greenish blue colour, changed to green by excess of the reagent. The colouring matter is not taken up by chloroform. The colour is destroyed by free acid, by heat, or by contact with alcohol.[1] Pseudomorphine also gives a blue colour with ferric chloride, and codamine a dark green.

2. Nitric acid (1·42 sp. gr.) added to solid morphia turns it an orange-red colour, which is changed to yellow on heating, and destroyed on adding sodium thiosulphate (hyposulphite). The

[1] The coloration is produced in strong solutions of morphine, but becomes imperceptible with moderate dilution. J. L. Armitage (*Pharm. Jour.*, [3], xviii. 761) has pointed out that even in solutions far too dilute to give the reaction, the morphine may be detected by adding potassium ferricyanide, which produces a blue or green coloration. Armitage attributes this reaction to the reduction of the iron to the ferrous state, and the reaction of this with the ferricyanide to form Turnbull's blue; but it is more probable that the ferricyanide is reduced to ferrocyanide, and then reacts with the ferric salt to form Prussian blue (compare page 317).

coloration is said to be due to the formation of a body of the formula $C_{10}H_9NO_9$, which yields picric acid when heated with water to 100°.

3. Solid morphine, when pure, is commonly said to yield no coloration in the cold on adding pure concentrated sulphuric acid; but according to Dott (*Pharm. Jour.*, [3], xii. 615) a distinct, though faint, pink colour is produced. On heating to 150°, a dirty green (or rose-red) colour is developed, and on raising the temperature still further the solution becomes almost black. On allowing it to cool and diluting with water, a greenish blue colour is produced, which on addition of ammonia in excess becomes green.

4. On adding *oxidising agents* to the solution of solid morphine in cold concentrated sulphuric acid, the following reactions are produced.[1] *a.* After adding a drop or two of water to heat the mixture, the subsequent addition of nitric acid will produce a rose-red coloration, changing to brown. The reaction is very delicate. *b.* Potassium chlorate gives reactions similar to those with nitric acid. If the alkaloid be first heated with concentrated sulphuric to 100° for half an hour, and a crystal of potassium chlorate or nitrate added to the previously cooled violet-red solution, a beautiful violet-blue colour is produced, which passes into a dark blood-red, changing to yellow. *c.* If the sulphuric acid solution be heated on the water-bath to 100°, and a minute fragment of pure potassium perchlorate[2] be added, a deep brown or reddish brown coloration is produced, which rapidly spreads through the liquid. The colour is destroyed on dilution. L. Siebold, to whom the test is due, did not observe a similar reaction with any other alkaloid. *d.* Potassium bichromate is reduced with production of green colour. (No colour-reaction is produced if for the bichromate be substituted the dioxide of lead or manganese. Distinction from strychnine.) *e.* On adding sodium or potassium arseniate, and warming gently, a slate-blue colour is produced, which on raising the temperature passes into green, then into deep blue, and finally, when the acid begins to volatilise, again into dark olive-green. On diluting moderately with water, a reddish brown coloration is produced, changing to dirty bluish and green on further dilution; and on agitating with chloroform the latter liquid is coloured violet-blue (Donath). If

[1] The reactions in question have been verified in the author's laboratory by W. H. Barraclough, and the description given in the text is in accordance with his results.

[2] The perchlorate must be free from chlorate, which is ensured by heating it with hydrochloric acid as long as chlorine is evolved. The salt is then washed with cold water and dried.

sodium phosphate be substituted for the arseniate[1] and heat applied till acid fumes appear, the mixture becomes violet, changing to brown or olive-green. If, after cooling, water be gradually added, a reddish brown coloration appears, changing to dirty bluish green on further dilution. On now shaking with chloroform, the latter liquid acquires a fine blue colour. *f.* Sodium or ammonium molybdate added to the sulphuric acid solution gives a fine violet coloration, changing to blue and dirty green, and finally almost vanishing. The reaction of morphine with sulphomolybdic acid may be observed with more certainty by adding previously prepared Fröhde's reagent (page 147) to the solid morphine. Papaverine and a few glucosides give a similar reaction.

5. If solid morphine be mixed with from 2 to 8 parts of powdered cane-sugar, or solutions of the two bodies be mixed and evaporated to dryness, addition of a drop of concentrated sulphuric acid will produce a beautiful purple colour, changing gradually to blood-red and brownish red, becoming olive-brown on dilution with water. The colouring matter is not soluble in chloroform. The test may be applied to a solution of morphine by saturating the liquid with sugar, and pouring it carefully on to some concentrated sulphuric acid, when a purple or rose-red coloration will be observed at the junction of the two fluids. Codeine gives a very similar reaction (Schneider). According to H. Weppen the delicacy of this test is much increased by adding a drop of bromine-water after the sulphuric acid, this modification rendering the reaction equal if not superior to reactions 3 and 4 *c*, and less dependent on the purity of the morphia.

M. Robin mixes the alkaloid with twice its weight of powdered sugar, and adds one or two drops of pure sulphuric acid, and states that morphine hydrochloride gives a beautiful rose colour, changing first to the tint of a solution of potassium permanganate, and then to violet and dark green, while codeine gives a cherry-red colour changing to violet, and narcotine a beautiful and very persistent mahogany-brown colour.[2]

B. *Reactions of Morphine in solution.* The following reactions

[1] For convenience, this test is described here, but it seems improbable that the reaction is due to oxidation.

[2] Atropine gives with sugar and sulphuric acid a violet coloration, changing to brown; veratrine, a deep green; santonin, a red colour, changing to coffee-black. Salicin gives a vivid red. Pure aconitine gives no reaction, but mixed aconite alkaloids as extracted from the root give a fine cherry-red coloration, changing to crimson. No reaction is given by strychnine, brucine, cocaine, pilocarpine, caffeine, beberine, apomorphine, cupreine, or the cinchona bases (J. F. Burnett).

are yielded by an aqueous solution of the hydrochloride or acetate of morphine :—

1. On adding to a tolerably concentrated solution of a salt of morphine a fixed caustic alkali, an alkaline carbonate, ammonia, or lime-water, hydrated morphine, $C_{17}H_{19}NO_3+H_2O$, is thrown down as a white precipitate speedily becoming crystalline. The precipitate is almost insoluble in perfectly cold water, but dissolves in excess of ammonia or lime-water, and very readily in excess of caustic alkali. The alkaline carbonates, used in excess, redissolve the precipitate somewhat, but it is insoluble in excess of bicarbonates. Excess of magnesia precipitates the alkaloid completely. The morphia precipitated by the foregoing reagents, and allowed time to become crystalline, presents a characteristic appearance under the microscope.

A fairly accurate determination of morphine may be made in the absence of interfering substances, by precipitating the tolerably concentrated, cold, aqueous solution with sodium bicarbonate, allowing time for the precipitate to become crystalline, filtering, washing moderately with very cold water (preferably saturated with morphine), drying at 100° or 120°, and weighing the anhydrous morphine, $C_{17}H_{19}NO_3$, when the weight becomes constant.

Instead of drying and weighing the alkaloid, the washed precipitate may be placed, together with the filter, in a moderate excess of standard acid, and the excess employed ascertained by titration with litmus or methyl-orange (not phenolphthaleïn). 1 c.c. of decinormal acid neutralises 0·0285 gramme of anhydrous morphine.

2. If morphia be liberated from the solution of a salt by one of the reagents mentioned above, and the liquid and suspended precipitate be at once shaken with hot amylic alcohol, cold acetic ether, or a mixture of equal measures of ether and acetic ether,[1] the morphia passes into solution, though with some difficulty, and may be obtained in a free state by separating the ethereal liquid, and evaporating it to dryness at a gentle heat. If the liberated morphia be allowed to crystallise before subjecting it to agitation with the solvent, its solution becomes very difficult to effect.

For quantitative purposes, hot amylic alcohol should be employed as the solvent. It should be added before the alkaloid is liberated, which should be done by ammonia, magnesia or sodium bicarbonate, and the agitation should be conducted immediately, and the separation and re-agitation effected without delay. On evaporation of the amylic alcohol at 100° the anhydrous morphine will remain as

[1] The acetic ether must be free from acid. This may be ensured by agitating it with some sodium bicarbonate before use.

a residue, which can be weighed,[1] or the amylic alcohol containing the alkaloid in solution may be titrated by dilute standard acid and methyl-orange, as described on page 131. If desired, the alkaloid may be recovered from its amylic alcohol solution by repeated agitation with dilute hydrochloric acid,[2] and then reprecipitated from the aqueous liquid by ammonia, or an alkaline bicarbonate. This affords a valuable means of purifying morphine and separating it from other alkaloids.

To effect complete extraction of the morphine liberated by magnesia, ammonia, or an alkaline bicarbonate, several agitations with amylic alcohol are necessary. If ammonia be employed, sufficient passes into the amylic alcohol to vitiate the subsequent determination of the morphine by titration; while if the amylic alcohol be freed from ammonia by agitation with water, or even with brine, a portion of the morphine is dissolved out. If the separated amylic alcohol be distilled off, the residual morphine may be titrated, or the difficulty avoided by using magnesia instead of ammonia.

3. A volumetric determination of morphine may be made by means of Mayer's solution, as described on page 140. The method has little practical utility.

Further information on the determination of morphine will be found in the section on the assay of opium.

4. Morphine readily reduces ferricyanides to ferrocyanides, with formation of pseudomorphine (oxydimorphine):—

$$4C_{17}H_{19}NO_3,HCl + 4K_3FeCy_6 = 2(C_{34}H_{38}N_2O_6,2HCl) + 3K_4FeCy_6 + H_4FeCy_6 .$$

Consequently, on adding to the solution of a salt of morphine, slightly acidulated with hydrochloric acid, a mixture of aqueous solutions of ferric chloride and potassium ferricyanide, a blue coloration or precipitate of Prussian blue is produced. This reaction may be conveniently employed for detecting morphine in presence of the cinchona bases.

L. Kieffer (*Annal. Chem. Pharm.*, ciii. 274) has proposed to utilise the reaction with ferricyanide for the quantitative determination of morphine. For this purpose he adds a known weight of solid potassium ferricyanide to the morphine or its salt, and mixes them in a mortar with a minimum quantity of water. The contents of the mortar are rinsed into a flask, potassium iodide and hydrochloric acid added, and the liberated iodine determined

[1] There is some evidence that morphine forms a compound with amylic alcohol not decomposed by evaporation at the ordinary temperature (*Pharm. Jour.*, [3], xviii. 161).

[2] A solution of morphine in hydrochloric acid cannot be shaken with amylic alcohol without extraction of some of the alkaloid, probably in the form of hydrochloride.

by decinormal sodium thiosulphate (hyposulphite). The difference between the volume required and that used in a blank experiment with the same weight of potassium ferricyanide corresponds to the salt reduced by the morphine. One c.c. of difference in the $\frac{N}{10}$ thiosulphate used represents ·0292 of anhydrous morphine.[1]

Venturini (*Gaz. Chim. Ital.*, xvi. 239) reports favourably of Kieffer's process. The author's results were discouraging.

5. On mixing a solution of morphine with one of iodine dissolved in hydriodic acid, a crystalline precipitate is formed even in extremely dilute solutions. Under the microscope the crystalline form is characteristic of morphine, which may thus be distinguished from papaverine and codeine, which bases also give crystalline precipitates with the reagent, while narcotine, narceine and thebaine yield amorphous precipitates.

6. Addition of chlorine or bromine water, followed by ammonia, occasions in moderately concentrated solutions of morphine a brown colour or red coloration gradually changing to brown.

7. Morphine and its salts reduce iodic acid with liberation of iodine. This reaction is also produced by albuminoid and various other organic bodies, so that it is not absolute proof of the presence of morphia. The test becomes much improved and increased in delicacy by the following mode of operating :—

To the solution to be tested for morphia, as nearly neutral as possible, is added one of iodic acid in 15 parts of water. In presence of 1 part of morphia in 20,000 of liquid a yellow coloration is observed. In moderately strong solutions of morphine addition of starch-liquor changes the yellow colour to blue, but not in solutions containing less than 1 per 1000. This is important, as with other reducing agents the blue colour is well marked in far more dilute liquids. On adding excess of ammonia to the yellow liquid the colour is discharged if due to foreign matter, but distinctly deepened if due to morphia. If a solution of morphine, which is too dilute to give a blue colour with iodic acid and starch, be mixed with these reagents, and some highly dilute ammonia allowed to flow from a pipette on to the surface of the liquid, two coloured rings make their appearance at the junction of the fluids. A blue ring is seen in the lower acid layer and a brown one in the upper alkaline portion. If a dilute solution of morphia be mixed with one of starch, and evaporated to dryness in a porcelain crucible at a gentle heat, and the residue, after cooling, be

[1] It is possible that Kieffer's process might be applied to the amylic alcohol solution of morphine, by agitating it with potassium ferricyanide solution. In such a case, ammonia, if present, would not interfere.

moistened with iodic acid, a blue colour will be produced in presence of 1–20,000 of a grain of morphia (A. Dupré).

Another way of employing the test is to agitate a solution of iodic acid with an equal measure of carbon disulphide, which should not become coloured even after adding a drop or two of dilute sulphuric acid and again shaking, If the solution to be tested for morphine be now added to the mixture, and the whole again shaken, the carbon disulphide will be found after separation to have a violet colour from dissolved iodine if morphine be present, and the depth of tint will afford an indication of the amount. Morphine can be recognised in this way in a single drop of paragoric or tincture of opium.

Stein and others have described a colorimetric method of estimating morphine, based in the iodic acid reaction.

In employing the iodic acid test it is essential that the reagent should not give free iodine on treatment with a drop of dilute sulphuric or acetic acid.

8. Solutions of morphine salts give no crystalline precipitate with either potassium chromate, thiocyanate (sulphocyanide) or ferrocyanide (distinction from strychnine).

Apomorphine, $C_{17}H_{17}NO_2$. When morphine or its hydrochloride is heated to 140°–150° C. in a sealed tube, with a large excess of strong hydrochloric acid, or with zinc chloride at 110°, it is converted into the hydrochloride of apomorphine, the formula of which base differs from that of the parent alkaloid by the elements of water, though its formation is probably attended by polymerisation. Apomorphine may be obtained in a state of purity by dissolving the contents of the tube in water, adding excess of acid carbonate of sodium, and agitating with ether or chloroform, in either of which apomorphine is freely soluble (difference from morphine). The ethereal solution is separated and shaken with a very little strong hydrochloric acid, when crystals of the hydrochloride of apomorphine are deposited. These are separated, washed with a little cold water, and purified by recrystallisation. From its aqueous solution of the hydrochloride, sodium bicarbonate precipitates free apomorphine as a snow-white amorphous substance, readily soluble in alcohol, ether, chloroform and benzene, which speedily turns green on exposure to the air. The changed alkaloid is partially soluble in water and alcohol with emerald-green colour, in ether with magnificent rose-purple, and in chloroform with fine violet tint. The colourless solutions of the unchanged substance soon acquire these tints. In its physiological effects, apomorphine differs from morphine in a very marked manner, being a prompt and non-irritant emetic. From 0·001

to 0·010 is the adult medicinal dose by the stomach. Dangerous and even fatal symptoms have followed the hypodermic injection of 0·012 gramme. Apomorphine gives a crimson-red colour with nitric acid, and brown with iodic acid, but (unlike morphine) yields a rose-red or amethystine colour with ferric chloride, changing to violet and black. The most delicate reaction of apomorphine is the production of a green coloration when the solution is rendered faintly alkaline with potassium hydrogen carbonate and exposed to the air. With a solution containing 1 part in 100,000, the green colour appears within ten minutes.

Apomorphine is said to be liable to be formed in old solutions of morphine hydrochloride, which consequently acquire emetic properties; but the statement is disputed by Dott, and requires confirmation (*Pharm. Jour.*, [3], xvi. 287, 299, 604; xvii. 80).

Apomorphine Hydrochloride, $C_{17}H_{17}NO_2HCl$, forms anhydrous, minute, shining crystals, which turn greenish on exposure to light and air. It is freely soluble in water and alcohol, forming a neutral solution, which turns green on boiling or standing, and keeps better if very faintly acid. The freshly-made aqueous solution should be colourless, or nearly so. It is generally held that if a 1 per cent. solution be emerald-green, the sample should be rejected for medical use; but D. B. Dott (*Pharm. Jour.*, [3], xxi. 916) has pointed out that the coloration is so intense that very little actual change is thereby indicated. Morrell found an old solution which had been exposed to light for three months to act quite effectively.[1]

Basic Associates of Morphine.

As already stated, opium contains a large number of bases, some of which are present in very minute amount, or are altogether absent from some samples. The names, formulæ, solubilities, and chief colour-reactions of these alkaloids have already been given (page 294 to 305), and morphine has been described at length (page 309). The following are additional facts respecting the less important bases of opium.

Codamine, $C_{20}H_{25}NO_4$, melts at 126° when crystallised from benzene, and 121° when separated from alcohol or ether. It forms large six-sided prisms, which can be sublimed. It dissolves moderately easily in hot water, giving an alkaline solution. Its salts, which are amorphous, give precipitates with caustic alkalies and

[1] Morrell finds that a patient who is made violently ill by $\frac{1}{8}$ grain of apomorphine hydrochloride administered hypodermically, can take $\frac{1}{6}$ grain thrice daily in the form of pills. Apomorphine acts as a powerful expectorant in cases of chronic bronchitis.

ammonia, soluble in excess of either reagent with nitric acid; codamine gives a dark green coloration with sulphuric acid, and in presence of a minute quantity of ferric chloride a greenish blue. For other colour-reactions and solubilities, see page 301 *et seq.*

CODEINE. Codeia. $C_{18}H_{21}NO_3$, or $C_{17}H_{17}NO(OH).OCH_3$. This base has the constitution of a morphine methyl-ester. The relation of codeine to morphine and synthesis therefrom are described on page 167. Its theoretical relations and constitution have been recently further investigated by Knorr (*Ber.*, xxii. 181, 1113) and Skraup and Wiegmann (*Monatsch*, x. 732). Codeine occurs in opium in proportions ranging from 0·1 to 1·0 per cent.[1]

Codeine crystallises from dry ether or carbon disulphide in small anhydrous prisms. From water it is deposited in well-defined octohedra or orthorhombic prisms containing 1 aqua and melting under boiling water to an oily liquid. Anhydrous codeine melts at 150°–155°, and solidifies to a crystalline mass on cooling. Codeine is somewhat soluble in water, requiring 75 to 80 parts of cold water, or 17 at the boiling-point. It is readily soluble in alcohol, ether, amylic alcohol, chloroform and benzene, but is almost insoluble in petroleum spirit (compare page 301). Codeine is as soluble in ammonia as in water, a fact utilised to separate it from morphine, but it is practically insoluble in excess of caustic potash or soda, and is precipitated by these reagents from its aqueous solution, if not too dilute.[2] Solutions of codeine are optically active, the rotatory power being much affected by the nature of the solvent, and the presence and proportion of free acid. In alcoholic solution $S_j = -136°$; in chloroform, $-112°$.

Codeine has a bitter taste, and resembles morphine in its physiological action. It is official in the British and several foreign *Pharmacopœias*, and is chiefly employed to allay restlessness, cough, and other symptoms for which opium is generally prescribed, and when the latter medicine is not tolerated. In phthisis, it appears to prevent and appease the tickling irritation of the cough, without deranging the digestion. It is an important remedy in diabetes,

[1] Codeine is usually isolated from opium by precipitating the aqueous extract by calcium chloride, evaporating and cooling the filtrate, redissolving the deposited crystals of the hydrochlorides in water, and precipitating the morphine by ammonia. From the filtrate, after concentration, the codeine can be recovered by treating by precipitating with caustic alkali, and purified by crystallisation from ether.

[2] The hydroxyl-group in the codeine molecule does not appear to be phenolic, as evidenced by the insolubility of the alkaloid in caustic alkalies, and its negative reaction with ferric chloride.

and is also recommended as an hypnotic in mental disease. The official dose is from $\frac{1}{4}$ to 2 grains. In larger quantities, codeine produces narcotism, often preceded by vomiting and occasionally by purging.

Codeine is a strong base, having a marked alkaline reaction, and forming crystallisable, soluble salts, which are neutral to litmus and methyl-orange. The free base precipitates solutions of lead, iron, copper, and certain other of the heavy metals.

Codeine Hydrochloride crystallises in radiated groups of prisms containing $BHCl + 2H_2O$, soluble in about 20 parts of cold water. The solution is lævo-rotatory ($S_j = -108°$). The crystals lose a portion of their water ($\frac{1}{2}$ aqua) readily, but the remainder is only driven off by many days heating at 100° (Schmidt, *Pharm. Jour.*, [3], xxi. 82), but easily at 120° (Dott). Hence the proportion of water in commercial samples of the salt is variable.

Codeine Phosphates. The salt $BH_3PO_4 + 2H_2O$ is obtained as a crystalline precipitate by adding codeine to a solution of phosphoric acid till the reaction is only faintly acid, and then adding excess of alcohol. When recrystallised from water the composition is unchanged, but the salt deposited from the solution in hot dilute alcohol contains $2BH_3PO_4 + H_2O$. Both forms lose their water at 100°, and are met with in commerce, as also a preparation containing excess of phosphoric acid. The usual composition of commercial codeine phosphate is $B_2H_3PO_4 + H_2O$ (Dott). If the salt turn grey or yellow at 100°, the presence of impurity is indicated. The phosphate is said to be the preferable form of employing codeine for hypodermic injections.

Detection and Determination of Codeine.

In its reactions and general characters codeine presents a strong resemblance to morphine, but is sharply distinguished by its ready solubility in ether and chloroform, and its precipitation by excess of caustic alkali. Codeine does not reduce iodic acid, and gives no coloration with ferric chloride. In strong nitric acid it dissolves to a yellow liquid which should not become red (difference from and absence of morphine). With pure sulphuric acid, codeine gives no coloration, but on warming, or very prolonged standing (several days) at the ordinary temperature, a blue colour is developed. This colour is produced if a trace of nitric acid, ferric chloride, or other oxidising agent be present, an arseniate being the preferable reagent. The blue coloration on warming with sulphuric acid and ferric chloride is apparently common to all ethers of the codeine class. Fröhde's reagent (page 147) is stated by some observers to produce a dirty green colour, soon becoming deep blue, and changing in twenty-four hours to yellow; according to others, a cherry-red tint, changing

to violet, is produced. L. Raby states that if solid codeine be stirred up with two drops of a solution of sodium hypochlorite, four drops of strong sulphuric acid added, and the whole mixed together, a splendid and persistent blue coloration results. Esculin was the only other substance (of thirty examined) which gave at all a similar reaction. Lafon uses a solution of 1 gramme of ammonium selenite in 20 c.c. of strong sulphuric acid, which gives a magnificent green colour with traces of codeine. Other reactions are given on pages 302 to 306.

Commercial codeine has been met with adulterated with *ammonium tartrate* (*Pharm. Jour.*, [3], xiv. 1035), which salt closely resembles it, but is distinguished from codeine by its insolubility in alcohol.

Claassen has based a method of determining codeine on the well-known fact that it completely decomposes morphine salts (*N.Y. Pharm. Rundschau*, 1890, 40; *Jour. Chem. Soc.*, lviii. 1198). The warm aqueous solution of the free base is treated with excess of morphine sulphate with frequent shaking, and allowed to stand in the cold for at least twenty-four hours, when the deposited morphine is filtered off, dried, and weighed (or titrated). The amount found, multiplied by 0·9868, represents the anhydrous codeine, or by 1·0412, the hydrated codeine ($C_{18}H_{21}NO_3+H_2O$). To separate morphine and codeine, the mixed bases, or their salts, are evaporated to dryness with excess of magnesia. The residue treated with water, and the liquid shaken repeatedly with ether free from alcohol, the ether distilled off, and the residue exhausted with hot water. In the resultant solution the codeine can be determined as above described.

Claassen (*loc. cit.*) has also pointed out that free codeine completely decomposes ammonium salts when heated with them, and has based on the fact a method of determining the alkaloid; but as morphine behaves in a similar manner, the fact has little practical value.

The simplest means of determining codeine and morphine in admixture is to precipitate the solution of the hydrochlorides with acid carbonate of sodium, and wash the dried precipitate with chloroform. The residue consists of *morphine*. The aqueous filtrate is treated with caustic soda, agitated several times with chloroform, the various chloroform washings and extracts united, evaporated, and the residual *codeine* dried at 110°, and weighed (D. B. Dott).

Pseudocodeine, $C_{18}H_{21}NO_3+H_2O$, was discovered by E. Merck in preparing apocodeine (*Arch. Pharm.*, ccxxix. 161). It is a strong base, crystallising in needles melting at 178°–180°. It is

lævo-rotatory, forms crystallisable salts, gives no reaction with ferric chloride, and has a physiological action similar to, but weaker than, that of codeine.

Apocodeine, $C_{18}H_{19}NO_2$, is said to be produced by heating codeine hydrochloride with a concentrated solution of zinc chloride for fifteen minutes. It is described as gummy, insoluble in water, soluble in alcohol and ether, and yielding amorphous salts. In physiological action it is a valuable expectorant and mild emetic. Apocodeine gives a characteristic blood-red colour with nitric acid. D. B. Dott doubts the existence of apocodeine, and states that commercial *apocodeine hydrochloride* is not of a very definite nature, being probably a mixture of an amorphous modification of codeine, polymerised bases, chlorocodide, and apomorphine. The physiological results appear to harmonise with this view (*Pharm. Jour.*, [3], xxi. 878, 916, 955, 996).

Methocodeine or *Dimethylmorphine*, $C_{17}H_{17}NO(OCH_3)_2$, is of interest merely from its theoretical relation to morphine, codeine and thebaine (compare page 296). It is a base forming hard brilliant laminæ melting at 119°, and yields with sulphuric acid a brown coloration, turning violet on addition of water.

Cryptopine, $C_{21}H_{23}NO_5$, occurs in but very small quantity in opium, and is precipitated on adding caustic soda to the mother-liquor from which codeine, narceine, thebaine and papaverine have been separated. It crystallises from alcohol in minute six-sided prisms. It is optically inactive, sparingly soluble in boiling alcohol, very slightly in benzene or petroleum spirit, but more readily in chloroform. When freshly precipitated it is soluble in ether, but slowly separates from the solution. (See also pages 301, 304.) Cryptopine and its salts have a bitter taste, and pungent cooling after-taste; they are hypnotic and mydriatic.

Cryptopine salts when dissolved in hot water usually produce on cooling a gelatinous mass, which is gradually changed to crystals. The *normal sulphate* does not crystallise; the *acid salt* gelatinises, as the solution cools, and the jelly shows but slight signs of crystallising, even after standing several weeks. The *acid oxalate* and *acid tartrate* are very sparingly soluble. Neutral cryptopine *meconate*, $(C_{21}H_{23}NO_5)_2C_7H_4O_7 + 10H_2O$, is insoluble in cold, and but slightly soluble in boiling water, and is probably the form in which the alkaloid exists in opium (*Pharm. Jour.*, [3], xviii. 250).

Deuteropine, $C_{20}H_{21}NO_5$, an alleged homologue of protopine and cryptopine, requires further examination.

Gnoscopine, $C_{34}H_{36}N_2O_{11}$, occurs in the mother-liquors of narceine. When recrystallised from boiling spirit the base forms long, thin, white needles, having a woolly appearance when dried.

It melts at 233°, decomposing at the same time, and burns with a smoky flame, leaving a skeleton of charcoal. In pure sulphuric acid, gnoscopine dissolves with slightly yellow colour, which becomes at once carmine-red upon addition of a trace of nitric acid, the colour being permanent. This reaction distinguishes the base from rhœadine, which becomes red with sulphuric or hydrochloric acid alone (*Pharm. Jour.*, [3], ix. 82). Gnoscopine hydrochloride gives a buff-coloured precipitate with platinic chloride. (See also page 301.)

Hydrocotarnine, $C_{12}H_{15}NO_3$, is formed from narcotine, together with meconin, by the action of nascent hydrogen. It volatilises partly unchanged at 100°, and forms readily soluble salts.

Lanthopine, $C_{23}H_{25}NO_4$, is obtained from the mother-liquors left from the preparation of morphine by the Robertson-Gregory process (see page 308). It is a weak base forming no acetate. It is coloured orange-red by nitric acid, and pale violet by sulphuric acid, the latter colour changing to a dark brown on heating. (See also pages 301, 304.)

Laudanine, $C_{20}H_{25}NO_4$, occurs with lanthopine. It has recently been prepared on a commercial scale by Merck from opium mother-liquors, but the yield is only one-third that of cryptopine. Laudanine crystallises from its solution in boiling alcohol in transparent granules or hexagonal prisms melting at 166°. Laudanine is lævo-rotatory, tasteless, and poisonous, the hydrochloride being bitter and resembling strychnine in its effects. It resembles morphine in dissolving in caustic alkali solutions, but the sodium-derivative is reprecipitated in glistening white needles on adding excess of caustic alkali. From its solution in caustic alkali laudanine is wholly unremoved by chloroform or amylic alcohol, but is extracted if precipitated by ammonia. Its phenolic character is further evidenced by the green coloration yielded with ferric chloride. Treatment with methyl iodide converts laudanine into a base chemically resembling codeine, and distinct from laudanosine. The solution of laudanine in pure concentrated sulphuric acid has only a very faint pink tint; the same acid containing iron yields a slightly deeper tint; but on heating either solution till the acid begins to volatilise, a violet coloration is obtained. With nitric acid, laudanine gives an orange-red colour. Laudanine is a strong base, having an alkaline reaction, and forms well-crystallised salts of a bitter taste. BHI is sparingly soluble in cold water, and BHCl easily soluble in water, but nearly insoluble in brine. (See also pages 301, 304.)

Laudanosine, $C_{21}H_{27}NO_4$, is homologous with laudanine, but is not produced by heating that base with methyl iodide. Laudano-

sine is isolated by conversion into its sparingly soluble hydriodide. It crystallises from benzene in needles melting at 91°. Both the free alkaloid and its salts taste very bitter, and are tetanic poisons. Laudanosine is dextro-rotatory. The solution is strongly alkaline. It gives no coloration with ferric chloride. (See also pages 301, 304.)

MORPHINE, $C_{17}H_{19}NO_3$, has already been fully described (page 309).

MECONIDINE, $C_{21}H_{23}NO_4$ (page 301), forms a brownish yellow amorphous mass, soluble with difficulty in ammonia, but readily in caustic alkalies. The base cannot be removed from its solution in caustic soda by agitation with ether, but is extracted from its ammoniacal and lime-water solutions. Meconidine is alkaline in reaction, and nearly destitute of taste; but yields very bitter, unstable salts. It is very easily decomposed by mineral acids, with production of a rose coloration. It is dissolved by strong sulphuric acid with an olive-green, and by nitric acid with an orange-red colour.

NARCEINE. $C_{23}H_{29}NO_9$; or $C_{13}H_{20}NO_4.CO.C_6H_2(OCH_3)_2.COOH$ (compare page 299). This base was originally discovered by Pelletier, who attributed to it the melting-point 92° C., but Hesse found it to melt at 145°. This latter figure, although subsequently corrected by Hesse himself, has been generally adopted by compilers, though Claus and Meixner found 162°; but E. Merck has shown (*Chem. Zeit.*, 1889, p. 525) that the ordinary commercial alkaloid of English manufacture melts between 150° and 160°, and the pure base at 170°–171°.[1] Narceine crystallises from water in long white prisms or delicate needles, containing $2H_2O$, which is driven off at 100°. It has a bitter taste, with styptic after-taste, and powerful hypnotic properties. It is optically inactive. It is very sparingly soluble in cold water or spirit, but dissolves very easily on heating. It is but slightly soluble in chloroform, and insoluble in ether and benzene. Narceine is precipitated on adding *ammonia or caustic potash to solutions of* its salts, but dissolves in excess of either reagent, and on addition of a large excess of caustic alkali is reprecipitated as an oily liquid.[2]

Narceine is a very weak base, the free alkaloid having a very feeble alkaline reaction to delicate litmus; the solutions of its salts may be titrated with litmus just as if the alkaloid were absent. The acetate is decomposed by water, and the base is said to be extracted by chloroform (but not by amylic alcohol) from liquids containing

[1] Dott states that the melting-point is indefinite, as partial decomposition occurs.

[2] Narceine containing a carboxyl-group, its solubility in alkalies is normal, but it seems probable that the oil precipitated by excess of caustic alkali is an alkaline narceinate rather than the free alkaloid.

even free mineral acids. BHCl forms needles or short stout prisms very easily soluble in water and alcohol, and melting with decomposition at 163°. Narceine liberated from the hydrochloride or other salts by ammonia retains hydrochloric acid with great persistency, and cannot be purified by recrystallisation from water or dilute alcohol. According to E. Merck (*Chem. Zeit.*, 1889, p. 525; *Pharm. Jour.*, [3], xix. 1034; xx. 481) narceine can best be obtained pure by crystallisation from water containing some ammonia or caustic alkali, but a considerable quantity remains in permanent solution. For therapeutic purposes, the presence of a small proportion of hydrochloride is of no consequence, and Merck considers that a preparation free from meconin, and so far freed from basic salt as not to melt below 165°, is sufficiently pure.

Chlorine-water, followed by ammonia, gives a blood-red colour with narceine, but many other substances (*e.g.*, tannin) behave similarly. Potassium bichromate gives a crystalline precipitate after some time. Iodine gives a brown precipitate in narceine solutions, but if ammonia be added to remove excess of iodine the precipitate is seen to be blue. Weak iodine solution colours narceine black-blue; in boiling water a colourless solution is obtained, but the crystals formed on cooling have a violet or blue colour. Sulphuric acid containing iodic acid gives with narceine a black coloration changing to red (see also page 302 *et seq.*).

"Meconarceine," according to E. Merck, is a preparation of a very variable character, of which one form consists of a yellowish liquid containing codeine, narceine, and an unidentified acid soluble in ether, but no meconic acid. In another case the "meconarceine" formed a white powder melting at 110°, and consisting of a mechanical mixture of narceine and meconic acid, which on adding water combine chemically, and the recrystallised products melt with evolution of gas at 126°, which is the melting-point of acid narceine meconate (*Pharm. Zeit.*, 1889, p. 90).

NARCOTINE, $C_{22}H_{23}NO_7$, occurs in opium in very variable quantity, the usual range being from 1·3 to nearly 11 per cent.; but some samples contain traces too minute to be recognised by the usual methods. Narcotine may be extracted from dried opium by ether or benzene, or by the same solvents from the precipitate produced by ammonia in the aqueous solution of opium.[1] It may be separated from narceine by precipitating the solution with excess of ammonia, when the narceine remains in solution.

Narcotine crystallises from alcohol or ether in colourless, transparent, glittering prisms or groups of needles, which melt at 170°,

[1] Opium from which the narcotine has been removed in this manner is now an article of commerce.

and resolidify at 130°, crystallising if cooled slowly. Above 200° narcotine is decomposed into meconin and cotarnine.[1] It is feebly narcotic, exhibiting poisonous effects only in somewhat large doses (1·5 to 3·0 grammes). The solid base is nearly tasteless, but the solutions are bitter. In the free state narcotine is lævo-rotatory, but the salts exhibit dextro-rotation.[2]

D. B. Dott has obtained the acetate, sulphate and hydrochloride of narcotine in a crystalline state; but the first of these salts is almost completely decomposed by solution, the base being precipitated and free acetic acid formed. The same reaction occurs when sodium acetate is added to a solution of narcotine hydrochloride (compare page 306). The hydrochloride and sulphate of narcotine are somewhat more stable, their solutions remaining clear even when largely diluted; but they react with litmus just as if the acid were uncombined,[3] and yield the narcotine to chloroform and similar solvents. These facts prove the basic properties of narcotine to be very feebly marked.

Narcotine meconate forms a syrupy solution, which on evaporation dries to a varnish which redissolves perfectly in water.

The caustic alkalies, alkali-metal carbonates, and ammonia throw down narcotine as a white crystalline precipitate, almost insoluble in cold water and in excess of the precipitants. It may be extracted from the alkaline liquid by chloroform or benzene, or less readily by ether or amylic alcohol. It is practically unaffected by petroleum spirit (compare page 301).

Narcotine is precipitated by the usual alkaloidal reagents, but the reactions are not very characteristic. With potassium thiocyanate it yields a crystalline precipitate readily soluble in acids, even in acetic acid. Iodised potassium iodide precipitates narcotine from extremely dilute solutions. Narcotine may be precipitated and titrated by Mayer's solution (page 139).

If a solution of narcotine in dilute hydrochloric acid be treated with bromine, a yellow precipitate is obtained, which dissolves on boiling; by gradually adding bromine-water, and boiling, a fine rose

[1] The constitution and decomposition-products of narcotine are described on page 298.

[2] Hesse found for the free alkaloid—

	Alcohol.	Chloroform and Alcohol.	Chloroform.
Concentration, . .	0·74	2	2 and 5
S_D, ...	−185°·0	−191°·5	−207·8

For a solution in "benzine" Dott and Peddie found $S_D = -229°$ (when c was 1·5), and for a solution in dilute oxalic acid, $S_D = +62°$.

[3] Narcotine hydrochloride is neutral to methyl-orange (Dott).

colour is produced, but is readily destroyed by excess of bromime. The reaction is characteristic. With chlorine-water, narcotine gives a yellowish green colour, turned orange by ammonia. Iodic acid gives no coloration with narcotine. If narcotine be mixed with twice its weight of cane-sugar, and the mixture moistened with strong sulphuric acid, a fine and persistent mahogany-brown coloration is produced, said by M. Robin to be highly characteristic. (See also page 302.)

OPIANINE, to which the formula $C_{21}H_{21}NO_7$ is attributed, is probably merely impure narcotine.

OXYNARCOTINE, $C_{22}H_{23}NO_8$, is contained in the mother-liquors of narcotine.[1] It forms minute crystals, somewhat soluble in hot water, but little soluble in hot alcohol, and insoluble in ether, chloroform or benzene. By oxidation with ferric chloride it yields cotarnine and hemipinic acid. $BHCl+2H_2O$ forms crystals. (See also page 101.)

PAPAVERINE, $C_{20}H_{21}NO_4$, is a weak base of feeble narcotic properties. It is separated from narcotine by crystallisation from a strong solution in oxalic acid, the *acid oxalate* of papaverine being very sparingly soluble. Papaverine crystallises in rhombic prisms or needles, or sometimes in scales. It is slightly lævo-rotatory,[2] though its hydrochloride is inactive. The neutral *succinate* forms large tabular crystals melting at 171°, and soluble in hot water; the *benzoate*, triclinic crystals melting at 145°, and soluble in alcohol but insoluble in water; and the *salicylate*, monoclinic crystals melting at 130°. Sulphuric acid containing iodic acid gives with papaverine a purple colour, turning black and green. Dilute solutions of papaverine salts are not precipitated by phosphomolybdic acid. Tincture of iodine, added to an alcoholic solution of papaverine, gives gradually a precipitate of crystalline needles. With potassio-iodide of cadmium, papaverine yields a dense white precipitate. (See also page 301 *et seq.*)

PAPAVEROSINE, found by Deschamps (1864) in the dried seed-capsules of the poppy, crystallised in prisms, was soluble in alcohol, ether, chloroform and benzene, and formed a gummy hydrochloride. With sulphuric acid it gave a violet coloration.

[1] Oxynarcotine was first isolated in an impure condition by D. Brown, from crude narceine. This product was purified and analysed by Alder Wright and Beckett.

[2] G. Goldschmidt (*Monatsch*, ix. 42) states that pure papaverine is inactive, and suggests that the optical activity of laudanine should be reinvestigated, as these two alkaloids constitute the only two known exceptions to the Bel-Van't Hoff theory that derivatives of optically active substances are also active.

Porphyroxine, described by Merck in 1837 as the red colouring matter of opium, according to Hesse is a mixture of several bases, one of which is meconidine, and another probably rhœadine, which latter alkaloid also occurs in the capsules and other parts of the red poppy. Kanny Lall Dey (*Pharm. Jour.*, [3], xii. 397) states that by treating the aqueous extract of Indian opium with ammonia or sodium carbonate, and immediately agitating with ether, the ethereal solution always leaves on evaporation a body (rhœadine ?) which, when warmed with dilute hydrochloric acid, gives a rich purple coloration, and he recommends the reaction as a test for Indian opium.[1] With Turkey and Smyrna opium no such reaction is obtained.

Protopine, $C_{20}H_{19}NO_5$, appears to be the most widely-distributed of all the opium alkaloids. It is found in very minute quantity in opium, but has been met with also in *Macleya cordata*, *Stylophorum diphyllum*, *Sanguinaria Canadensis*, and *Chelidonium majus*. Protopine resembles cryptopine, but the solutions of its salts have a bitter taste, and do not gelatinise on cooling. In small doses, protopine acts on frogs as a narcotic, and in stronger doses paralyses the muscle-substance, and the peripheral ends of the nerves. Upon mammals it has a poisonous action like that of camphor, but differs from it in paralysing the circulating organs. (See also pages 301, 304.)

Pseudomorphine. Oxydimorphine. $C_{34}H_{36}N_2O_6$.[2] This alkaloid is best purified by solution in ammonia, from which it crystallises in colourless crusts or delicate silky needles containing 3 aqua. It is a very weak base, forming no acetate, and is without action on vegetable colours. It is tasteless and not poisonous. It dissolves readily in caustic alkalies and milk of lime, but is insoluble in all the ordinary alcoholic and ethereal solvents, as also in dilute sulphuric acid and alkaline carbonates. (Compare page 301.) Its most soluble salt is the hydrochloride, which requires 70 parts of cold water for solution. On adding ammonia, avoiding excess, the alkaloid is precipitated in a crystalline state from the hot, and in a gelatinous state from the cold solution. Hesse finds that when pseudomorphine is mixed with an equal weight of cane-sugar, and

[1] Merck repeatedly dips a slip of filter-paper in the ethereal solution, allowing it to dry spontaneously after each immersion. The paper is then moistened with hydrochloric acid and exposed to steam, when it will acquire, especially after drying, a more or less distinct rose-red colour.

[2] Pseudomorphine occurs very rarely, having been observed by Hesse in good Smyrna opium only once in four years. It may be prepared by treating morphine with oxidising agents of moderate power, such as potassium ferricyanide or dilute permanganate (page 144).

strong sulphuric acid (pure) added, a characteristic dark green coloration is obtained, which gradually turns brown (compare test 5, page 315). If the acid contain a minute quantity of iron, a blue coloration changing to green is produced.

RHŒADINE, $C_{21}H_{21}NO_6$, exists in all parts of the red poppy (*Papaver Rhœas*), and in the ripe seed-capsules of the white poppy. It forms small white prisms, which are tasteless and not poisonous. Its solutions in weak acids, avoiding excess, are colourless, but on adding excess of sulphuric or strong hydrochloric acid a purple-red colour is produced. This is destroyed by alkalies and restored by acids, and is so intense that 1 part of rhœadine will colour 10,000 parts of water purple-red, 200,000 deep rose-red, and 800,000 distinctly red, although only a fraction of the base is converted into colouring matter. The colourless solution of rhœadine in acids is precipitated by tannin. On adding potassium iodide to a solution of the acetate, the hydriodide is precipitated as a dense crystalline mass, consisting of microscopic prisms. An aqueous solution of rhœadine becomes red by prolonged boiling, part of the alkaloid being converted into the isomeric base r h œ a g e n i n e (soluble without colour in acids), and on adding a drop of hydrochloric or sulphuric acid the whole base is decomposed, the solution acquiring a purple-red colour. Cold dilute sulphuric acid converts solid rhœadine into a colourless resinous mass, which soon dissolves with splendid purple colour, changing to dark purple on boiling, and depositing on cooling small prisms which are brownish red by transmitted and green by reflected light; while the liquid retains rhœagenine equal to 99 per cent. of the rhœadine present, together with the colouring matter.

Opium sometimes contains a base which gives the above colour-reactions with sulphuric acid, but it is somewhat doubtful if it is actually rhœadine. (Compare Porphyroxine, page 330.)

THEBAINE, $C_{19}H_{21}NO_3$, or $C_{17}H_{15}NO(O.CH_3)_2$. Thebaine occurs in opium in proportions ranging from 0·15 to 1·0 per cent. It crystallises in silvery scales from dilute alcohol, and in needles or hard quadratic prisms from strong alcohol. Thebaine melts at 193°, and is not sublimable.[1] It has a sharp and styptic taste, and is a powerful tetanic poison, producing symptoms resembling those due to strychnine. The fatal dose is smaller than that of morphine. Thebaine gives a reddish brown coloration with chlorine-

[1] *This is Hesse's experience, and is confirmed by Dott.* According to other observers, at about 135° it sublimes without fusing, and is deposited in minute crystals resembling caffeine; while at higher temperatures, needles, cubes, and prisms are obtained.

water and ammonia. Its other colour-reactions (and its solubilities) have already been described. (See page 301 *et seq.*)

Thebaine is stated to be extracted (with some difficulty) by chloroform from its acid solutions; but the statement requires confirmation, as it is inconsistent with the strongly-marked basic characters of thebaine.[1] From narcotine, thebaine may be separated by treating the concentrated acetic solution with excess of basic lead acetate, which precipitates the narcotine only. Dilute acids readily alter thebaine, converting it into the isomeric bases thebenine and thebaicine, which are sparingly soluble in hot alcohol and insoluble in other simple solvents. When heated to 90°, under pressure, with fuming hydrochloric acid, thebaine yields a base having the probable formula $C_{17}H_{15}NO(OH)_2$, called by its discoverer, W. C. Howard (*Ber.*, xvii. 527; xix. 1596), morphothebaine, to indicate its origin and relation to morphine.

TRITOPINE, $C_{42}H_{54}N_2O_7$, was isolated by Kauder in minute quantity from the mother-liquors of the opium-alkaloid manufacture. It resembles morphine and laudanine in being soluble in soda solution, but is reprecipitated in the form of an oil by a large excess of the reagent. Tritopine crystallises in characteristic anhydrous, transparent, needle-like plates melting at 182°, easily soluble in chloroform, but only slightly in ether. With sulphuric acid it behaves like laudanine. It appears to be a di-acid base (*Arch. Pharm.*, ccxxviii. 419).

Opium.

Opium is a gummy mass, consisting of the inspissated juice from the incised unripe fruit-capsules of *Papaver somniferum*, hardened in the air.

Opium is produced in Turkey, Asia Minor, Persia, India, China, and other countries, but Smyrna, Constantinople, or Turkey opium is the only variety recognised by the majority of the pharmacopœias. Persian and East Indian opiums are imported chiefly as sources of the opium alkaloids.[2] Chinese opium is wholly consumed locally.

[1] It is possible that certain thebaine salts are soluble in chloroform (as are those of codeine), and are dissolved as such by agitating their aqueous solutions with chloroform.

[2] The variety of poppy cultivated in Asia Minor is said to be the *black*, which usually has purple flowers, and black, though occasionally white, seeds. It is said to be usually richer in morphia than that from the *white*-flowering and white-seeded poppy, which is rich in narcotine, and appears to be the only kind cultivated in Egypt, Persia, India, China, and Japan. (For a chemical distinction between Turkey and Indian opium, see page 330.)

Opium varies considerably in appearance, composition, and quality, according to its origin and mode of preparation.[1]

Opium is remarkable for the large number of definite, highly complex, crystalline principles contained in it. Of these the majority are alkaloids, a list of which is given on page 204. In addition, opium contains acetic, lactic, and meconic acids, the last substance being peculiar to opium. Besides these bodies and the inorganic constituents, opium also contains the indifferent bodies meconin, meconoiosin, and opionin, and a variety of sugar; together with gummy and pectous matters, albumin, wax, fat, caoutchouc, resin. and a humoïd acid. Woody fibre and other extraneous matters are also frequently present; but genuine opium is wholly free from both starch and tannin.

The following may be taken as the *general* composition of opium:—

	Per Cent.		Per Cent.
Morphine,	6 to 15, average 8	Fat,	1 to 4
Narcotine,	4 to 8	Gum and soluble humoïd acid matters,	40 to 56
Other alkaloids,	0·5 to 2	Insoluble matters and mucus,	18 to 20
Meconin,	under 1	Ash,	4 to 8
Meconic acid,	3 to 8, average 4	Water,	8 to 30, average 20
Peculiar resin and caoutchouc,	5 to 10		

ALKALOIDS. *Morphine* is the most abundant of the bases of opium, and the most valuable of the constituents. Most of the pharmacopœias require dried opium to contain not less than 10 per cent. of morphine. *Good* Smyrna opium deprived of water usually contains from 12 to 15 per cent. of morphine, though cakes from the same case are apt to vary considerably; but if the proportion be below 10 per cent. on the dry substance, adulteration may be suspected. Egyptian opium is poorer in morphine than that from Asia Minor, the proportion ranging from 6 to 12 per cent., but it contains a larger proportion of narcotine. Persian opium is extremely variable in quality, probably partly in consequence of the practice of mixing it with sugar and other adulterants, though much of it is equal to ordinary Turkish opium. East Indian opium is, as a rule, remarkably weak in morphine, the proportion being

[1] The product of Asia Minor is described in the *British Pharmacopœia* (1885) as follows:—"In rounded, irregularly formed, or flattened masses, varying in weight, but commonly about eight ounces to two pounds, usually covered with portions of poppy leaves, and scattered over with the reddish-brown chaffy fruits of a species of Rumex. When fresh, plastic and internally somewhat moist, coarsely granular, and reddish- or chestnut-brown, but becoming harder by keeping, and darkening to blackish-brown. Odour strong, peculiar, narcotic, taste nauseously bitter."

sometimes as low as 2½ per cent., more commonly between 3½ and 5, and occasionally as high as 8 or 9 per cent. This inferiority is probably partly due to climate and partly to defective methods of collection and preparation.[1] The variety known as "Patna garden opium" is prepared specially for medical use, and contains from 7 to 8 per cent. of morphine. In Chinese opium, the proportion of morphine is generally low. French opium yielded Guibourt from 14·4 to 22·8 of morphine, and German from 16·5 to 20 per cent.; that from the white poppy containing, according to Biltz, 6·8 per cent. (?) Algerian opium from red poppies yielded 10·4 to 17·8 per cent. of morphine, and from white poppies 1·5 to 8·5 per cent. (?) In United States opium, the proportions of morphine observed have ranged from 7·4 to 10·2 per cent.

The morphine in opium is usually stated to exist in combination with meconic acid, but Dott has shown that morphine ordinarily exists in opium partly as meconate and partly as sulphate.[2] In some cases traces of acetate and lactate are present.

Narcotine exists in opium in widely varying proportions and often in considerable abundance. Upwards of 10 per cent. has been occasionally met with. East Indian opium always contains more narcotine than morphine, whilst French opium sometimes affords neither narcotine, narceine, nor thebaine.

The narcotine in opium is generally assumed to be uncombined, as it is readily extracted by treating the original (dried) substance with ether or benzene; but as narcotine is readily removed from the acidulated solutions of most of its salts by agitation with a suitable solvent, such as chloroform or benzene, it does not follow that its extraction from opium is due to its presence in a free state. It most probably usually exists as meconate. Occasionally the narcotine resists the action of solvents, unless the sample of opium has been previously treated with ammonia.[3]

[1] Aubergier states that in one case the product contained 18 per cent. of morphine, while the opium from a neighbouring farm, where the collection was made somewhat later, contained only 11 per cent.

[2] *Pharm. Jour.* [3], xiv. 389. This conclusion is based on the following observations:—1. An alcoholic extract of opium contains sulphuric acid, which cannot be in combination with alkaloids, as metallic sulphates are insoluble in alcohol. 2. An aqueous extract of opium contains sulphuric acid in quantity sufficient to combine with the whole of the morphine. 3. The same extract contains meconic acid in quantity insufficient to convert all the morphine into meconate. 4. The same extract contains inorganic and organic bases with which the sulphuric acid will unite in preference to the morphine, and the remainder of the sulphuric acid will not suffice to combine with all the morphine. (See also *Proc. Roy. Soc. Edin.*, 1882–83, page 189.)

[3] Twelve samples of opium analysed by Flückiger (*Pharm. Jour.* [3],

Porphyroxine, according to Kanny Lall Dey (*Pharm. Jour.*, [3], xii. 397), is a definite basic substance, always present in Indian opium, but absent from Turkey or Smyrna opium. Dey regards its presence as so constant and characteristic of Indian opium that he utilises it in toxicological investigations. (See page 330.)

The *other alkaloids* of opium have been observed in the following proportions :—

Codeine, 0·2 to 0·4 per cent.
Codamine, 0·003 per cent.
Cryptopine, very small.
Lanthopine, 0·005 per cent.
Laudanine, 0·005 per cent.
Narceine, 0·02 to 0·1 (0·7) per cent.[1]
Papaverine, 1·0 per cent.
Pseudomorphine, 0·02 per cent.
Rhœadine, minute.
Thebaine, 0·15 to 1·0 per cent.[1]

MECONIN. Opianyl. $C_{10}H_{10}O_4$, or $C_6H_2 \left\{ \begin{array}{l} O.CH_3)_2 \\ CO.O \\ CH_2 \end{array} \right\}$

Meconin is an indifferent body, crystallising in colourless, shining, six-sided prisms, which melt under water at 77° C., or alone at 110°, and distil at 155°. It is odourless, bitter, and readily soluble in alcohol and chloroform, but only sparingly in ether.

v. 845) gave the following analytical results. The proportions of morphine are most probably sensibly below the truth.

Description of Opium.	Ethereal Extract, consisting of		Pure Narcotine.	Morphine.	
	Wax.	Crude Narcotine.		Crude.	Pure.
1. Patna,	14·2	10·0	4·0	11·2	8·6
2. Indian (1852–53),	12·7	9·0	6·1	11·2	4·3
3. Akbari,	13·5	8·5	5·5	14·2	3·5
4. Behar,	13·0	7·6	4·5	10·6	4·6
5. Malwa,	6·5	7·6	4·7	14·4	6·1
6. Synd,	9·4	8·0	3·1	...	3·8
7. Hyderabad,	10·7	9·7	5·4	...	3·2
8. Candeish,	...	...	7·7	...	6·1
9. Persian,	14·8	10·2	6·4	...	7·1
10. Egyptian,	11·5	12·2	3·7	...	5·8
11. Playford, Suffolk (1823),	8·8	9·3	6·0	...	4·3
12. English (1859),	12·0	11·6	8·1	...	8·3

Assays of thirty-eight samples of opium, published by M. Adrian, showed a proportion of morphine exceeding 7 per cent. in all but two cases, the average being 10 per cent. The narcotine averaged 2·5 per cent., but bore little relation to the proportion of morphine. A sample showing only 3·87 per cent. of morphine contained 3·45 of narcotine, while other samples contained over 10 per cent. of morphine and only the same percentage of narcotine. This variation is doubtless the reason why some samples of opium cause little or no headache and others occasion very disagreeable symptoms.

[1] **Narceine often occurs more abundantly than thebaine.**

Meconin may be readily crystallised from boiling water, in which it is moderately soluble.

The meconin contained in opium, in which it exists in the proportion of less than 1 per cent., is probably a decomposition-product of narcotine, from which base it may be prepared by heating with nitric acid.

Meconin is extracted from its acidulated aqueous solution by agitation with benzene, chloroform, or amylic alcohol, the first-named solvent being preferable. Meconin dissolves in concentrated sulphuric acid, without at first producing any coloration; but the solution gradually assumes a greenish tint, changing to reddish in the course of twenty-four hours. If the liquid be then warmed, the colour changes to emerald-green, blue, and purple, finally becoming red. The shades and order of the colours obtained depend much on the proportion of acid used, the tints being bluer and the reaction more delicate with a small quantity. Evaporated with slightly diluted sulphuric acid, meconin gives a green coloration. In concentrated hydrochloric acid it dissolves without change of colour, even on heating. If meconin be dissolved in strong sulphuric acid and a minute fragment of potassium nitrate added, a yellow coloration is obtained, rapidly changing to a fine scarlet, which fades slowly and is changed to yellow on heating. The reaction is delicate.

An aqueous solution of meconin gives precipitates of characteristic microscopic appearance with iodised potassium iodide and a solution of bromine in hydrobromic acid (T. G. Wormley).

MECONOIOSIN, $C_8H_{10}O_2$, was obtained in brown, leaf-like crystalline masses from the mother-liquors left on the isolation of meconin. When pure it is colourless, freely soluble in alcohol, ether, and hot water, fuses at 88°, and on evaporation with somewhat diluted sulphuric acid yields a red colour, changing to purple.

OPIONIN, according to Hesse, is contained in small quantities in Smyrna opium. It forms white needles which melt at 227° and contain no nitrogen. It is insoluble in water, but dissolves in alkalies, alcohol, and ether. When boiled with milk of lime, opionin is decomposed, an acid being formed which is freely soluble in water and ether, and gives a bulky precipitate with lead acetate in alkaline solutions.

MECONIC ACID, $C_7H_4O_7 = C_5HO_2(OH):(CO.OH)_2$. This substance is characteristic of opium, in which it exists chiefly in combination with the alkaloids, but sometimes a portion of it appears to be present in a free state.

Meconic acid may be prepared from opium by precipitating the neutralised aqueous solution of the drug with calcium chloride,

ltering, and decomposing the precipitate of calcium meconate by repeated treatment with warm diluted hydrochloric acid. A preferable plan is to precipitate the aqueous solution of opium with neutral lead acetate, filter, suspend the precipitate in water, and decompose it with a stream of sulphuretted hydrogen. The filtered and concentrated solution deposits meconic acid on addition of hydrochloric acid. The product may be purified by re-solution in hot water, cooling, and adding hydrochloric acid. Meconic acid may also be conveniently prepared by precipitating it as the calcium salt, decomposing this with a slight excess of oxalic acid, filtering, and concentrating.

Meconic acid crystallises in micaceous scales or small rhombic prisms containing 3 aqua. On being heated to 100°, it loses its water of crystallisation and leaves a white effloresced mass. At 120° C. it splits up into carbon dioxide and comenic acid, $C_6H_4O_5$, which at a higher temperature again loses carbon dioxide, and forms pyromeconic acid, $C_5H_4O_3$.[1] Comenic acid is but sparingly soluble in hot, and is almost insoluble in cold water. In absolute alcohol it is quite insoluble. Meconic acid dissolves in 115 parts of cold, or 4 parts of boiling water; its solubility in the cold is diminished by addition of hydrochloric acid, which therefore causes a precipitate in strong solutions. When the solution of meconic acid is boiled for some time, especially if hydrochloric acid be present, comenic acid is formed, and crystallises out as the liquid cools. The aqueous solution of meconic acid has a sour astringent taste, and strongly acid reaction.

Meconic acid is freely soluble in alcohol (distinction from comenic acid) and is deposited in fine crystals on spontaneous evaporation of the solution. It is much less readily soluble in ether and is almost wholly insoluble in chloroform.

Nitric acid readily acts on meconic acid, much oxalic acid being formed.

Meconic acid derives its chief analytical interest from the fact that it is *strictly peculiar to opium* and its preparations, and hence

[1] The relationship between these three bodies appears to be as follows:—

$$C_5HO_2\begin{cases}OH\\CO.OH\\CO.OH\end{cases}\qquad C_5HO_2\begin{cases}OH\\H\\CO.OH\end{cases}\qquad C_5HO_2\begin{cases}OH\\H\\H\end{cases}$$

Meconic acid. Comenic acid. Pyromeconic acid.

Comenic acid forms prisms, laminæ or granules, insoluble in alcohol, soluble in 16 parts of boiling water, but deposited on cooling.

Pyromeconic or pyrocomenic acid contains no carboxyl-group, and its acid characters are very feebly marked. It crystallises in prisms, is readily soluble in water and alcohol, melts at 117°, and boils at 227°; but sublimes slowly at the ordinary temperature and readily at 100°.

its positive detection is a decided proof of the presence of a preparation of opium. It is not poisonous.

The microscopic appearance of the precipitates produced in not too dilute solutions of meconic acid or soluble meconates by barium chloride, calcium chloride, potassium ferrocyanide, and hydrochloric acid are highly characteristic.

The most characteristic reaction of meconic acid is the formation of a deep purplish red coloration on adding ferric chloride to the solution of meconic acid or a meconate. The shade of colour is distinctly different from that of the ferric *acetate* or *formate*, and the ferric meconate also differs from these in not being readily destroyed by boiling, or by adding cold dilute hydrochloric acid, and from the ferric *thiocyanate* in being unaffected on addition of mercuric chloride or auric chloride.[1] If any doubt exist as to the presence of an acetate, it is desirable to precipitate the neutralised solution with nitrate or neutral acetate of lead, wash the precipitated lead meconate thoroughly, suspend it in water, and decompose it with sulphuretted hydrogen. After evaporating the filtered liquid at a gentle heat to drive off the excess of sulphuretted hydrogen, the test with ferric chloride may be safely applied. Instead of adding ferric chloride to the solution of meconic acid, the reagent may be applied to the solid substance, as obtained by the evaporation of its aqueous or ethereal solution.

The red coloration produced by meconic acid and a ferric salt is much weakened by oxalic and phosphoric acids, and still more so by metaphosphoric acid.

Comenic and pyromeconic acids also strike a red coloration with ferric chloride, but with the latter acid the colour is less deep.

Meconic acid may be extracted from its acidulated solutions by agitation with ether, a property which enables it to be readily separated from morphine, acetic acid, tannin, and other substances liable to interfere with the observance of its reaction with ferric chloride. The extraction is not perfect, even when several times repeated, and hence the method cannot be employed for quantitative purposes.

Meconic acid may be determined by converting it into a lead salt, or colorimetrically by ferric chloride, by comparing the depth of tint produced by the sample with that obtained by treatment with a known quantity of opium. Very fair approximate estimations of meconic acid, and less accurately of opium, may be made in this way, even when the quantity of material at disposal is very insignificant.

Three of the atoms of hydrogen in meconic acid are replaceable

[1] Thiocyanates (sulphocyanides) exist in sensible quantity in the saliva (and hence in the contents of the stomach) and also in white mustard.

by metals, but recent researches have shown that the acid is, properly speaking, dibasic, only two carboxyl groups, CO.OH., being present. The third atom of hydrogen belongs to hydroxyl, and when this is replaced by metals basic salts of a yellow colour result.

The *metallic* meconates are mostly insoluble in water, except the meconates of the alkali-metals. They are nearly all insoluble in alcohol, and are but slightly affected by acetic acid. The salts having two atoms of basic hydrogen replaced by metals are neutral to litmus paper.

Acid Calcium Meconate, $CaH_2[C_7H(OH)O_6]_2$, is precipitated as a sparingly soluble salt of characteristic microscopic appearance on adding calcium chloride to not too dilute a solution of meconic acid or a soluble meconate. In presence of free ammonia, less soluble, yellow, *dicalcic meconate*, $Ca_2[C_7H(OH)O_6]_2$, is precipitated. On treating either of these salts with hot dilute hydrochloric acid, meconic acid crystallises out on cooling.

Iron Meconates. Ferrous meconate is a colourless, very soluble salt, which turns red on exposure to air. Ferric meconate exists in the purple-red liquid produced on adding a ferric salt to a soluble meconate.

Lead Meconate is obtained by precipitating meconic acid or a meconate (or an aqueous solution of opium) with neutral acetate of lead. The triplumbic meconate is stated to be formed even in presence of excess of meconic acid, but it is more probably a mixture or compound of the normal meconate, $PbC_7H_2O_7$, with lead hydroxide. The precipitate is quite insoluble in cold and boiling water, and is not affected by acetic acid.

Morphine Meconate has already been described (page 313).

ACTION OF SOLVENTS ON OPIUM.

The action of different solvents and reagents on opium and its constituents is shortly as follows:—

Water dissolves meconic acid readily, as also sulphate, meconate, and acetate of morphine. The morphine is very sparingly soluble in cold water, and narcotine still less so. Narceine is much more soluble than morphine, while the resin, caoutchouc, &c., are insoluble, though certain gummy matters pass into solution.

Alcohol dissolves free morphine as well as the acetate and meconate. The other alkaloids of opium, as also the resin and caoutchouc, are dissolved by alcohol.

Amylic alcohol dissolves all the alkaloids of opium, if in a free state. The resin also is slightly soluble in amylic alcohol.

Ether, benzene, and *carbon disulphide* dissolve only about ·05 per cent. of free morphine, but the other free alkaloids of opium more readily. These solvents also dissolve the caoutchouc, but not the resin.

Acids dissolve all the alkaloids from opium, together with a resinoid substance.

Fixed alkalies, used in excess, dissolve morphine freely, while narcotine remains insoluble. Lime water dissolves morphine, but is a solvent for narcotine only in presence of morphine. The resin of opium is partly soluble in alkalies.

Ammonia dissolves morphine sparingly, narceine and codeine readily, while the other alkaloids and the resin of opium are insoluble.

From the foregoing statements, the arrangement of which is mostly due to E. L. Cleaver (*Year-Book Pharm.*, 1876, page 502), it follows that an *aqueous solution* of opium will contain sulphate and meconate of morphine and other alkaloids, calcium salts, meconic acid, extractives, and resinous matter.

An *alcoholic solution* will contain, in addition to the above, free narcotine, caoutchouc, fat, and resin.

Opium which has been exhausted with water still retains a bitter taste, but this is probably due to narcotine, as it is removed by carbon disulphide, benzene, or ether, in which morphia and its salts are insoluble. Water, even when cold, may be trusted to dissolve the whole of the morphine from opium, if the resultant solution be distinctly acid. In some processes of assaying opium, the sample is subjected to a preliminary treatment with *benzene*, *chloroform* or *ether* to remove narcotine, caoutchouc, and colouring matter (see page 349). By this means the subsequent exhaustion with water is much facilitated, and a purer solution of morphine is obtained. In presence of much narcotine, morphine is soluble in benzene, but this is not true of the sulphate, meconate, or other *salts* of morphine. Hence there is no loss of morphine on extracting opium with benzene. Meconate of morphine is, however, freely soluble in a mixture of alcohol and chloroform; but the simultaneous presence of ether prevents its solution more or less completely.

ADULTERATIONS AND ASSAY OF OPIUM.

Opium is liable to a variety of adulterations, some of which are of a very gross kind. Sand, clay, ashes, stones, shot, bullets, lead turnings and other make-weights are occasionally met with. Sugar, gum tragacanth, pulp of apricots and figs, pounded poppy-capsules, and other vegetable substances of a saccharine, mucilaginous, and resinous nature are also employed. Aqueous extracts of poppies and of *Glaucium luteum* are said to be sometimes added in Turkey, though rarely if ever seen in the opium imported into England. Such adulterants are indicated by the darker colour and hygroscopic character of the product, by the difficulty in filtering the solution, and by the continuous streak which the sample leaves when drawn

across a sheet of paper, whereas good opium makes an interrupted mark.

The proportion of *ash* yielded by opium should not exceed 8 per cent. The proportion of *water* in opium averages about 20 per cent., the usual range being from 15 to 28 per cent. It is best determined by taking a known weight of the opium in thin slices, and noting the weight on drying at 100° C.

The *extract* of opium is determined by exhausting the dried sample with cold water, and collecting, drying, and weighing the residue; or evaporating the whole or an aliquot part of the solution to dryness, and weighing the extractive matter left. Should the insoluble residue exceed 40 to 45 per cent. of the *dried* sample (equal to a minimum of 55 per cent. of extract), the presence of sand, clay, or other insoluble (mineral) adulterants is probable; while if the residue is below this proportion the presence of sugar, gum, or other soluble impurity is indicated.[1]

[1] *According to* Hanbury *and* Flückiger, *dried opium from Asia Minor* should yield from 55 to 66 per cent.—generally more than 60—of extractive matter soluble in cold water, the proportion of extract from Indian opium being from 60 to 68 per cent.

The following are determinations by D. B. Dott (*Year-Book Pharm.*, 1876, page 498) of the leading constituents of eighteen samples of opium, purchased from druggists of good standing in London, Dublin, and Edinburgh. The aqueous extract was determined by subtracting the sum of the water and insoluble matter from 100·00. The proportion of morphia calculated on the dried opium averaged 11·06 per cent. The proportion of morphia in the dry extract was 18·3 per cent. (compare page 350.)

Description of Opium.	Percentage Composition.			Percentage of Morphine (hydrated).
	Water.	Insol. Residue.	Aqueous Extract.	
1. Turkey,	19·6	32·60	47·80	10·75
2. ,,	20·0	28·85	51·15	12·80
3. ,,	26·0	25·95	48·05	10·20
4. ,,	21·2	23·70	55·10	7·57
5. ,,	22·0	30·95	47·05	9·60
6. ,,	18·4	25·45	56·15	11·69
7. ,,	19·2	25·90	54·90	12·80
8. ,,	20·4	34·20	45·40	12·80
9. ,,	27·2	35·80	37·00	6·75
10. ,,	21·2	38·80	40·00	9·80
11. ,,	22·8	29·70	47·50	8·55
12. ,,	31·2	47·90	20·90	6·93
13. Persian,	14·0	26·80	59·20	6·00
14. ,,	12·0	27·40	60·60	8·50
15. ,,	16·0	25·90	58·10	2·10
16. Malwa,	15·2	24·10	60·70	7·80
17. ,,	13·6	25·20	61·20	5·88
18. Egyptian,	14·8	28·30	56·90	7·00
Average,	19·70	29·86	50·44	8·88

Hager recommends the following additional tests for the purity of opium:—25 grains weight of the previously dried sample is triturated with half an ounce of boiling water, when the formation of a stiff paste will indicate the presence of starch, flour, gum, &c. 2 ounces of water should next be added and the liquid filtered. If the filtrate be brown or of a deeper colour than "wine-yellow," the presence of liquorice or other vegetable extracts is probable. The liquid should have an acid reaction, or admixture with chalk, litharge, or ashes may be suspected. The liquid should give no reaction with potassium ferrocyanide (heavy metals), and if evaporated to one ounce and treated with twice its measure of alcohol no precipitate should be produced (indicative of adulteration with gum or certain salts).

On agitating powdered opium with chloroform, any starch or mineral adulterants will settle out, and may be weighed and further examined microscopically and chemically.

When moist, opium is very liable to become mouldy, and hence should be dried at a moderate temperature and carefully preserved from the air. If kept in a damp condition, fungoid growths soon make their appearance, and gradually diminish and destroy the aroma of the opium, besides materially reducing its alkaloidal value.

DETERMINATION OF MORPHINE IN OPIUM. MORPHIOMETRY.

By far the most important item in the examination of opium is the determination of the morphine present. The proportion of this constituent varies considerably, as already stated; but dried and powdered opium intended for medicinal use should not assay *less* than 10 per cent.[1] This is the limit of the German and Austrian Pharmacopœias, while that of the United States allows the range of 12 to 16 per cent., any richer opium to be reduced within these limits by mixing it with an article of lower grade in proper proportion. According to the German and United States Pharmacopœias, opium in its normal moist condition should yield not less than 9 per cent. of morphine. The British Pharmacopœia of 1867 allowed a range of 6 to 8 per cent.; but in the edition of 1885 the assay is directed to be made on the dried substance, the yield of morphine to be between 9½ and 10½ per cent.[2]

[1] The difficulty caused by the natural variations in the quality of opium is well met by a process patented by B. S. Proctor, who removes the greater part of the fatty and resinous matters and the worthless narcotine, and reduces the opium to a uniform rectified condition, in which it contains 10 per cent. of morphine.

[2] "This standard is ridiculously low, and will have the effect of depriving medicine of all the best opium that reaches this country. This standard is about equal to that of the last Pharmacopœia; but then there was no maxi-

The assay of opium for morphine has received much attention, the investigators being very numerous and the bibliography very extensive. The accurate determination of morphine in opium is attended with peculiar difficulties, and many of the processes which have been published give little better than rough approximations to the truth, especially when employed for the assay of abnormal samples.[1] Of the many methods proposed, the following are among the best:—

British Pharmacopœia Process.[2]—This method of assay is based on:—the conversion of the resinous matters of opium into insoluble lime compounds; the decomposition of the morphine meconate with formation of insoluble calcium meconate; the solubility of the resultant free morphine in lime-water; the decomposition of the solution by ammonium chloride, with formation of calcium chloride, ammonia, and free morphine; the use of alcohol to dissolve impurities, and of ether to promote the crystallisation of the alkaloid; and the collection, washing, and weighing of the morphine thus obtained. The following are the details of the process as laid down in the British Pharmacopœia of 1885:—

"Take of powdered opium, dried at 212° F. (= 100° C.), 140 grains; lime, freshly slaked, 60 grains; chloride of ammonium, 40 grains; rectified spirit, ether, distilled water, of each a sufficiency. Triturate together the opium, lime, and 400 grain-measures of distilled water in a mortar until a uniform mixture results; then add 1000 grain-measures of distilled water, and stir occasionally during half an hour. Filter the mixture through a plaited filter about 3 inches in diameter into a wide-mouthed bottle or stoppered

mum standard given. It is all very well to standardise preparations, but, I think, it is going too far when we attempt it with natural products; but if we are to have a maximum and minimum standard for opium, let it be one which will include the best and exclude the inferior and adulterated kinds, instead of the reverse, as now obtains. To attain this it would be necessary to raise the standard *at least* 2 per cent."—(Michael Conroy, *Pharm. Jour.*, [3], xvi. 378.)

[1] The sampling of opium for the purpose of analysis is not always an easy operation, and is not conducted on a uniform plan. J. B. Nagelwoort recommends that a small slice should be cut by a knife from the interior of each lump of the lot, these pieces mixed together, and 10 grammes taken for the determination of moisture. The remainder is dried, pulverised, and the residual moisture and morphine determined in it.

[2] This method was originally devised by Portes and Langlois (*Chem. News* xlv. 67), and with slight alterations was adopted by the Société de Pharmacie of Paris, and made official in the United States Pharmacopœia of 1880. It was further improved by M. Conroy (*Pharm. Jour.*, [3], xv. 473), and adopted as the official test in the British Pharmacopœia of 1885.

flask (having the capacity of about six fluid ounces, and marked at exactly 1040 grain-measures) until the filtrate reaches this mark.[1] To the filtered liquid (representing 100 grains of opium) add 110 grain-measures of rectified spirit, and 500 grain-measures of ether, and shake the mixture; then add the chloride of ammonium, shake well and frequently during half an hour, and set it aside for twelve hours.[2] Counterbalance two small filters; place one within the other in a small funnel, and decant the ethereal layer as completely as practicable upon the inner filter. Add 200 grain-measures of ether to the contents of the bottle and rotate it; again decant the ethereal layer upon the filter, and afterwards wash the latter with 100 grain-measures of ether added slowly and in portions. Now, let the filter dry in the air, and pour upon it the liquid in the bottle in portions, in such a way as to transfer the greater portion *of the crystals to the filter. When the fluid has passed through* the filter, wash the bottle and transfer the remaining crystals to the filter, with several small portions of distilled water, using not much more than 200 grain-measures in all, and distributing the portions evenly upon the filter. Allow the filter to drain, and dry it, first by pressing between sheets of bibulous paper, and afterwards at a temperature between 131° and 140° F. (55° and 60° C.), and finally at 194° to 212° F. (90° to 100° C.). Weigh the crystals in the inner filter, counterbalancing by the outer filter. The crystals should weigh 10 grains, or not less than 9½, and not more than 10½ grains, corresponding to about 10 per cent. of morphine in the dry, powdered opium."

The skilled chemist will find abundant opportunity for improving on the method of manipulation prescribed in the above process. He will probably substitute their equivalents in grammes and centimetres for the weighed and measured grains prescribed; but he will, in practice, find it advantageous to increase the weights of opium and lime taken to 10 grammes and 5 grammes respectively, and the measure of the water to 100 c.c. 52 c.c. of the filtrate will then represent 5 grammes of the opium, and the delay, consequent on collecting so large a portion as ⅘ of the

[1] The additional 40 grain-measures is intended as an allowance for the average increase in the volume of the liquid caused by the extractive matter of the opium.

[2] "The use of an excess of ether, much beyond ether-saturation, so as to cause an ethereal layer to rise above the crystallising liquid, along with the frequent shaking up of the ether with the aqueous liquid in the closed flask during crystallisations, marks an important advance in opium assay."—(A. B. Prescott.) The practice has been adopted in all recent methods of assaying opium.

e avoided.[1] A less clumsy means will be adopted for ıe exact quantity of the filtrate required than that of mark made on the side of a 6 oz. bottle, or the broad k; and the ethereal layer will be removed by some te instead of attempting to decant it on the filter.

process for the assay of opium is tolerably simple nd when carefully executed, gives fairly constant suggested by Conroy, and proved by Braithwaite time allowed for precipitation of the morphine may om twelve hours to two without affecting the accuracy s, but it is safer to allow six or eight hours to elapse g. It would be a further improvement to direct that should be titrated instead of being weighed.[2] This guarantee of the true nature and purity of the pre- would save the time required for, and uncertainty the drying of the alkaloid.

s yielded by the B.P. process of assaying opium are w the truth, a fact ignored by the editors, although y M. Conroy, whose process it practically is.[3]

aite and Farr (*Pharm. Jour.*, [3], xvii. 398) ›y's view, and state that the morphine left in solution er cent. of the opium. But they point out that the ntains an average of 7 per cent. of colouring matter

y states that, by reducing the quantities of opium and water y him, the editors of the Pharmacopœia have deprived the of its chief merits, with the consequence that the 1040 grain-rate required can only be obtained at the sacrifice of much braham (*Pharm. Jour.*, [3], xvi. 380) endorses this view, or the sake of saving a few grains of opium, a simple and quick ı rendered most tedious. The standard of 10 per cent. was, ' that he had not yet succeeded in getting any genuine Turkey gh to stand it." (For the reply of the editor (J. Attfield) er damaging criticisms, see *Pharm. Jour.*, [3], xvi. 470.)

the precipitated morphine was directed by Portes and original proposers of the method (*Jour. Pharm. et Chemie*,

› the Pharmacopœia, from 9½ to 10½ grains of crystals should ıined, "*corresponding to about ten per cent. of morphine in* ered opium," a statement which is materially inaccurate. , in test-experiments on 10 grains of pure morphine, 9·05, grains were recovered, thus showing a notable but almost The loss when an aqueous extract of opium is operated on, solution of morphine, is still greater, probably ranging from t. Hence a yield of 9½ to 10½ per cent. of morphine, by ıa, not improbably corresponds to about 11½ per cent. of y present.

as impurity, and hence, in assaying an opium containing 14 to 15 per cent. of morphine, the error from this cause approximately balances that due to imperfect precipitation.[1] On dissolving the impure morphine in lime-water, a large proportion of the colouring matter is left in the filter, and on extracting the solution with ammonium chloride, alcohol and ether, as in the B.P. process, the rest of the colouring matter remains in solution, and the reprecipitated morphine is obtained almost white. But there is a serious loss (10 per cent. of the weight) through solubility of the precipitate.

J. Denham Smith (*Chem. News*, lvii. 93, 103) obtained by the B.P. process, in five experiments, results ranging from 9·4 to 9·6 per cent., a sixth experiment giving 10·5 per cent., the true amount of morphine present being stated at 11·2 per cent., which was obtained by a process giving exceptionally high results (page 347). Smith distrusts the use of lime as open to many objections, and this opinion is shared by R. Williams[2] (*Chem. News*, lvii. 134), who gives the following results obtained from four samples of opium when assayed by the processes of the British, American, and German Pharmacopœias respectively.

	No. 1.	No. 2.	No. 3.	No. 4.
British, ...	10·8	10·5	7·4	12·2
American, ...	11·1	10·8	8·1	11·9
German, ...	10·2	10·0	7·1	10·6

In each case the German process gave the lowest result,[3] and the American the highest, except in the case of No. 4 sample.

[1] Dott considers 7 per cent. of impurity excessive, and thinks 3 to 5 per cent. would be nearer the truth.

[2] Notwithstanding this, D. B. Dott (*Pharm. Jour.*, [3], xix. 83) considers that the employment of lime "has much to be said in its favour. It gives a purer solution of morphine than can be obtained by any other single operation, and besides eliminates nearly all possible adulterants. The morphine precipitated by the ammonium chloride is usually remarkably pure, we might say *always* if the opium is genuine. Samples are, however, occasionally met with which yield with the chloride of ammonium a certain amount of flocculent precipitate along with the morphine. In such cases it is pre-eminently necessary to apply the titration with standard acid. There can be no doubt that the editors of the Pharmacopœia ought to have allowed for the inevitable loss of morphine in the mother-waters, especially when any other trustworthy method is permitted."

[3] Various observers agree that the results obtained by the German method of assay are at least 2 per cent. below the truth, and the morphine not always pure (*Pharm. Jour.*, [3], xiv. 645).

The yield of morphine obtained by the B.P. process ought to be corrected by a definite allowance, but a more satisfactory plan would be to prescribe a method by which the remaining alkaloid could be recovered if desired. This might probably be approximately effected by agitating the warm ammoniacal filtrate with amylic alcohol, and separating and evaporating the solvent.

United States Pharmacopœia Process.—As already stated, the method of opium assay prescribed by the British Pharmacopœia is a modification of that previously adopted in America. The latter differs from the B.P. process chiefly in prescribing the use of a larger proportion of ammonium chloride. This is a distinct disadvantage as tending to retain morphine in solution, a fact pointed out by M. Conroy, and confirmed by Wrampelmeier and Meinert.[1]

Method of Teschemacher and Denham Smith.—These chemists have examined most of the published methods of assaying opium (*Chem. News*, lvii. 93, 103), and have found them wanting in one or more respects. They reject methods in which the precipitation of the morphine is effected in presence of more than a very limited amount of alcohol (*e.g.*, Fluckiger's older methods) as likely to yield low results, though a very pure product; they object to the use of lime (as in the B.P. product) as causing the product to be coloured, and being open to other objections; and they strongly advocate the titration of the morphine isolated, instead of determining it gravimetrically. All these objections are well founded, though scarcely so vital as they are regarded by the authors, who, however, have described a method of assay which, on the whole, is probably the best hitherto published.[2] The process they recommend is

[1] These latter chemists calculated the amount of ammonium chloride which would remain in excess, and free ammonia which would be produced in the reaction, and ascertained their solvent action on morphine; but the correction *logically based on their results would be seriously in excess of the actual loss* of morphine in practice. H. Lloyd has proposed to correct the results obtained by the U.S. process by adding 5 per cent. to the amount of morphine (or multiplying it by 1·05), and making an additional correction of 1 per cent. to the morphine thus found. Thus, if 9·0 per cent. of morphine be actually recovered, according to H. Lloyd, the true amount present is $9·0 \times 1·05 + 1·0 = 10·45$ per cent. Similarly, H. Goebel (*Jour. Chem. Soc.*, lii. 869) recommends an allowance of 0·001 gramme for each c.c. of liquor and washing, and points out certain defects in the U.S. process which may be overcome by modified manipulation.

[2] This view is confirmed by D. B. Dott, who operates as follows:—10 grammes weight of the powdered opium is exhausted with proof spirit, one or two drops of ammonium oxalate are added, and then ammonia, until the spirit is only slightly acid. The liquid is then evaporated to one-third, allowed to

founded on one originally devised by Prollius and modified
F. A. Flückiger (*Archiv. der Pharm.*, [3], xxvi.). It was t
materially improved by E. R. Squibb (*Ephemeris*, i. 14),
again further modified by C. M. Stillwell (*Chem. News*,
41, 54). The following are the details of the process as prescri
by Teschemacher and Smith:—200 grains weight of opiun
thoroughly exhausted with warm distilled water,[1] and the liq
filtered. The aqueous extract is concentrated to a thin syrup
shallow dish, over a water-bath, which by preference should
boil. The syrup is transferred to a suitable flask, and the
washed out with a few drops of water. To the contents of
flask are added 50 fluid grains of alcohol (specific gravity ·8
and about 600 fluid grains of ether. A soft cork is inserted
the contents of the flask mixed gently but thoroughly, after wl
50 fluid grains of ammonia (specific gravity ·935) should be ad
The flask is then well shaken to precipitate the alkaloid in ar
ceous crystals, and occasionally agitated during the ensuing eigh
hours. The contents of the flask are then transferred to a vacu
filter, and when all the adherent liquid is drawn out the crystal
precipitate is washed with "morphiated spirit"[2] until the li
passes through colourless. It is then washed with "morphi
water"[2] until this also passes colourless. The precipitate is t
dried, at first slowly and afterwards at 100° C. The dried
stance is then finely powdered and digested thoroughly in ben
to dissolve the narcotine and such other opium alkaloids as ma
present in addition to morphine.[3] The liquid is filtered and

cool, and filtered. The filtrate is concentrated to about 5 c.c., transferre
a small flask, and the capsule washed with 4 c.c. of water and 3 of methy
spirit. Next add 2·2 c.c. of ammonia solution (sp. gr. ·960) and 25 c.
ether, and agitate. After 18 hours, decant the ether as completely as poss
receive the aqueous liquid on a counterpoised filter, wash with morph
water, dry, wash with benzene, dry, weigh, and titrate the whole or a po
with decinormal sulphuric acid (*Pharm. Jour.*, [3], xxii. 746).

[1] Rowland Williams digests with cold water for twelve to fourteen h
and claims to obtain a cleaner solution than when warm water is used.

[2] The "*Morphiated Spirit*" is made by mixing 1 measure of amm
(specific gravity ·880) with 20 of methylated spirit, and digesting in the li
a large excess of powdered morphine for several days, with frequent agita
The filtered liquid contains 0·33 per cent. of morphia. "*Morphiated W*
is made by agitating cold water with excess of morphine, and filtering
twenty-four hours. The filtrate contains 0·04 per cent. of alkaloid.

[3] Seeing that the morphine is ultimately determined by titration, that
cotine, narceine, and papaverine have no action on litmus, and that co
is soluble in 80 parts of cold water and readily soluble in alcohol and e
the prescribed treatment with benzene in order to remove these alka
seems superfluous. When the morphine is to be weighed, it would prob

precipitate further thoroughly washed with benzene. The residue will consist of morphine "free from other opium alkaloids and narcotine, but still containing colouring and possibly other organic matters to the extent of 3 to 10 per cent." (of its weight). The powder is dried, weighed, and titrated with litmus and a standard hydrochloric acid, prepared so that 1000 grains by weight will exactly neutralise 100 grains of pure morphine crystallised from water, washed with ether, and gently dried at 100° C.

Flückiger's process. F. A. Flückiger has devoted much attention to the assay of opium, his most recent method (*Archiv. Pharm.*, [3], xxvii. 721, 769 ; *Pharm. Jour.*, [3], xx. 588) being as follows: —8 grammes weight of powdered opium is placed in a plaited filter, and dried at 100° for half an hour. It is then treated with 20 c.c. of a mixture of equal measures of ether and chloroform, and when this has run through, with 10 c.c. of unmixed chloroform. The filter and its contents are then dried at a gentle heat, and the powder vigorously and repeatedly shaken in a flask with 80 c.c. of water to which 0·2 gramme of ammonium oxalate has been added. After two hours the liquid is passed through a dry filter, and 42·5 grammes of the filtrate (=4 grammes of sample) treated in a small tared flask with 7½ c.c. of rectified spirit, 15 c.c. of ether, and 1 c.c. of ammonia (specific gravity 0·96). The mixture is frequently shaken during six hours, after which the liquid is poured on a double filter, the flask rinsed with 10 c.c. of water or morphiated water, and the rinsing used to wash the filter. The precipitate and inner filter are dried at 100°, returned to the dried flask, and the whole further heated to 100° till constant, the outer filter being used as a counterpoise. The foregoing process would be materially improved and shortened by titrating the dried morphine instead of weighing it on a counterpoised filter, and its accuracy increased by reducing the quantities of liquid used. J. B. Nagelvoort (*Pharm. Jour.*, [3], xxi. 598) has slightly modified the above method, which he commends very highly, for the assay alike of opium and its galenical preparations. He found the isolated alkaloid to be completely soluble in 100 parts of lime-water to a clear, colourless solution, whereas the "morphine" obtained by Squibb's and Stillwell's modifications of Flückiger's former process contained from 10 to 20 per cent. of impurities.[1]

be better to wash with morphiated spirit only, and when it is to be titrated to omit this treatment and wash it at once with benzene.

[1] If narcotine be present it is left as a crystalline residue on treating the alkaloid with lime-water. Perger has proposed to purify morphine by dissolving it with dilute acetic acid and adding potassium ferrocyanide, filtering, and precipitating the morphine from the filtrate by ammonia.

L. Kieffer, in 1857, described a volumetric process of assaying opium, based on the reaction of the morphine with potassium ferrocyanide, reaction of the excess of this salt with potassium iodide, and titration of the liberated iodine with standard thiosulphate (*Annal. Chem. Pharm.*, ciii. 280). A limited number of experiments made in the author's laboratory on Kieffer's process have not yielded encouraging results.

Extract of Opium, B.P., is made by exhausting the opium with cold water, straining, and evaporating the liquid to half the weight of the opium used. It has a pilular consistency,[1] and is said to yield about 20 per cent. of morphine when assayed by the official test for opium. W. P. Want (*Pharm. Jour.*, [3], xvi. 959) found by this process from 9·9 to 20·4 per cent. of morphine in six samples of the commercial extract of opium.[2] By the method of the 1867 Pharmacopœia, D. B. Dott found in eleven samples of extract, purchased from druggists of good standing in London, Dublin and Edinburgh, proportions of morphine ranging from 15·4 to 22·8 per cent., the mean being 19·7.

Liquid Extract of Opium, B.P., is prepared by macerating 1 ounce of the solid extract with 16 ounces of water, adding 4 fluid ounces of rectified spirit, and filtering. It should contain "22 grains of the solid extract in nearly 1 fluid ounce." The specific gravity should be between 0·985 and 0·995, and when assayed by the process prescribed for opium "should yield about 1 per cent. of morphine."

J. Woodland (*Year-Book Pharm.*, 1882, p. 514) found in ten samples of the liquid extract of opium of commerce proportions of solid residue ranging from 3·02 to 4·92 per cent., and of morphine from 0·19 to 0·37 per cent. These determinations were made by a modification of Prollius' method, the accuracy of which was demonstrated. D. B. Dott (*Year-Book Pharm.*, 1876, 500) found the specific gravity of eleven samples of commercial fluid extract to range from 0·985 to 1·000, while the proportion of morphine per fluid ounce varied from 1·66 to 4·51 grains.

Tincture of Opium. Laudanum. For the preparation of this important medicine, the *British Pharmacopœia* directs to "macerate 1½ ounces of opium in powder in 1 pint of proof spirit for

[1] The United States Pharmacopœia orders an addition of 5 per cent. of glycerin.

[2] J. H. Hoseason (*Pharm. Jour.*, [3], xix. 754) has pointed out that extract of opium is sold by wholesale druggists at a cheaper rate than they can purchase the opium for its preparation.

seven days in a closed vessel with occasional agitation, then strain, press, filter, and add sufficient proof spirit to make one pint. It contains the soluble matter of 33 grains of the opium, nearly, in 1 fluid ounce, or about 3·3 grains of morphine in 1 fluid ounce, or about 0·75 per cent. of morphine, or about 1¼ per cent. of bimeconate of morphine,[1] besides the other alkaloidal salts of opium."[2] No specific gravity is given, and no method of testing the preparation is prescribed; but it is evident that the method employed for the assay of opium may be applied, after evaporating off the spirit.

W. P. Want (*Pharm. Jour.*, [3], xvi. 959) found the specific gravity of six samples of tincture of opium procured from leading wholesale houses to range from ·931 to ·939. The proportions of morphine were estimated (in duplicate) by the official process for opium (using about 3 ounces of the tincture), and were found to be respectively:—3·34, 3·3, 2·6, 3·3, 3·4, and 2·18 grains per fluid ounce. All six samples were very similar in appearance and odour.

J. H. Hoseason (*Pharm. Jour.*, [3], xix. 754) has published the following results of the examination of ordinary commercial samples of tincture of opium:—

[1] This statement of the condition of existence of the morphine is without warrant, and is opposed to the known facts. The very existence of "bimeconate of morphine" is doubtful, and a large proportion of the morphine in opium exists as sulphate.

[2] The *Tinctura Opii* of the United States Pharmacopœia (1882) is prepared from powdered opium (assaying 12 to 16 per cent. of morphine) 10 parts, water 40 parts, alcohol (specific gravity ·820) 16 parts, and sufficient dilute alcohol (specific gravity ·928) to make the tincture obtained by percolation up to 100 parts. All the ingredients are by weight.

The *Tinctura Opii Simplex* of the German Pharmacopœia (1890) is prepared from powdered opium (with 10 per cent. or more of morphine) 1 part, diluted alcohol (specific gravity ·892 to ·896 at 15° C.) 5 parts by weight, and water 5 parts. It has a specific gravity of ·974 to ·978, and contains, in 100 grammes, the soluble portion of nearly 10 grammes of opium, or approximately 1 per cent. of morphine. 40 grammes when assayed should yield not less than 0·38 gramme of morphine.

The corresponding preparation (*Tinctura Extractæ Opii*) of the French Codex (1884) is prepared from 10 parts of extract of opium (= 16·7 of dry opium) containing 10 to 12 per cent. of morphine, and 120 parts by weight of alcohol of ·912 specific gravity.

From these particulars it is evident that the strength of the official tinctures of opium vary considerably, both in alcoholic strength and the proportion of morphine. The United States and French preparations are the strongest (in alkaloid), the German weaker, and the British the most dilute.

Number.	Specific Gravity.	Absolute Alcohol; per cent. by weight.	Residue; grs. per fluid ounce.	Morphine; grs. per fluid ounce.
1	·964	38	18·5	3·5
2	·952	40	17·0	3·0
3	·942	41	20·5	5·0
4	·940	42	14·5	2·0
5	·962	36	15·3	2·0
6	·960	37	17·3	3·0
7	·961	37	15·0	2·0
8	·966	35	18·5	2·5
9	·961	38	14·6	2·7
10	·946	40	18·0	3·0
Average, . .	·955	38·4	16·4	2·8

Six of the above samples were evidently made with a mixture of equal measures of rectified spirit and water, instead of the proportion of 5 : 3, which would yield approximately proof-spirit.

J. Woodland (*Year-Book Pharm.*, 1882, page 514) found the solid residue from fourteen samples of tincture of opium procured from both London and provincial chemists to range from 3·21 to 5·11 per cent.; while the morphine (estimated by a modification of Prollius' method) ranged from 0·32 to 0·70 per cent.

D. B. Dott (*Year-Book Pharm.*, 1876, page 500) found the specific gravity of twelve samples of the commercial tincture of opium to range from ·922 to ·962; while the crude morphine (estimated by a modification of the B.P. 1867 method, and averaging $\frac{7}{10}$ of pure alkaloid) contained in the same specimens, and six others (the density of which was not observed), ranged from 4·37 to 0·55 grains per fluid ounce, the average being 2·66.

From the foregoing published results it is evident that the composition of commercial tincture of opium varies to a very discreditable extent, both in alcoholic strength and the proportion of morphine contained in it. Still greater variations in strength are to be found in the tincture when purchased under the head of "laudanum," which, however, is now an official synonym for tincture of opium.[1]

S. J. Hinsdale (*Chem. News*, lxii. 77) has described a simple

[1] Several prosecutions have occurred under the Sale of Food and Drugs Act for the sale of defective tincture of opium. In the case of White *v.* Bywater, it was sold under the official name to the written order of a medical man. The court accepted the view of the defence, that, as the preparation contained alcohol, it was a "tincture," and that if it contained any opium at all it was a "tincture of opium," which, consequently, might be of any strength whatever. This decision was reversed on appeal to the Court of Queen's Bench (*Pharm. Jour.*, [3], xvii. 966).

method of determining the morphine in tincture of opium by observing the depth of the blue or green coloration produced on treating the sample with a freshly prepared mixture of ferric chloride and potassium ferricyanide solutions.

Compound Tincture of Camphor, B.P., is the formal designation of the preparation popularly known as "Paregoric," or "Paregoric Elixir." These names were adopted as official synonyms for compound tincture of camphor in the reprint of the *British Pharmacopœia* of 1885, and hence preparations sold under these titles ought now to be strictly of the quality and strength of the B.P. tincture. Compound tincture of camphor is directed to be prepared with 40 grains each of opium and benzoic acid, 30 grains of camphor, and 30 minims of oil of anise; the whole being diluted with proof-spirit to 20 fluid ounces.[1]

Much of the paregoric or compound tincture of camphor of commerce is deficient in one or more of the constituents. The spirit being the most costly ingredient, there is a strong inducement to the vendor to reduce its amount, a practice which is objectionable because the prescribed proportion of oil of anise cannot be kept in solution in a very weak spirit. Sometimes only traces of oil of anise are present, in which case the tincture remains clear when diluted with three or four measures of water. The benzoic acid is sometimes deficient in quantity, and occasionally wholly absent, even in the case of tinctures purchased from registered pharmacists. The opium is the most important constituent of paregoric elixir, and is apt to be deficient in amount or quality, besides being frequently wholly omitted. The last practice is due to the fact that preparations of opium cannot be legally sold except by registered pharmacists; and hence a preparation destitute of opium is largely substituted by general shopkeepers for the genuine "paregoric" or "compound tincture of camphor" sold by the druggists.[2] In an instance within the personal experience of the author, the opium of paregoric elixir was replaced by henbane. Potassium and ammonium bromides are extensively used in factitious paregoric.

The proportion of *alcohol* in compound tincture of camphor is

[1] W. D. Mason (*Pharm. Jour.*, [3], xii. 396) points out that great saving of time and trouble in maceration, agitation, filtering, &c., could be effected, and a perfectly clear and bright tincture, practically the same as that of the Pharmacopœia, obtained by adding the opium in the form of a ready-made tincture.

[2] So-called "paregoric" is vended by costermongers in the streets of London.

indicated with approximate accuracy by the specific gravity, which should not be higher than 0·926.[1]

If a measured quantity (25 c.c.) of paregoric be rendered distinctly alkaline with soda, and evaporated to about 10 c.c., the alcohol and a portion of the camphor and oil of anise will be volatilised. On then shaking the liquid with ether, the remaining camphor and oil of anise will be extracted. If the ether be separated, and the aqueous liquid acidulated with hydrochloric acid, benzoic acid will in some cases be precipitated; but whether it separates or remains in solution, it should be dissolved out by agitating the acidified liquid with ether. On allowing the separated ethereal solution to evaporate spontaneously in a small beaker, the benzoic acid is obtained in a state fit to weigh;[2] but a better and more rapid plan is to repeatedly agitate the ethereal liquid with water until the washings no longer redden litmus, add a little more water and a few drops of phenolphthaleïn solution, and titrate the liquid with $\frac{N}{20}$ caustic alkali (preferably baryta-water), which should be added until the aqueous layer acquires a pink colour, not destroyed by agitation with the ether. Each 1 c.c. of $\frac{N}{20}$ alkali required represents 0·0061 gramme of benzoic acid. If 25 c.c. of the tincture has been employed, the number of milligrammes of benzoic acid found, multiplied by 0·35, gives the grains of benzoic acid per pint of the tincture. The meconic acid extracted together with the benzoic acid is too small in quantity to affect the result, but its presence may be detected and the amount roughly determined by separating the ethereal layer after the titration is complete, and destroying the pink colour of the aqueous liquid by a drop of dilute hydrochloric acid. On now adding a drop of ferric chloride solution, the deep purple-red coloration characteristic of meconic acid will be produced.

The detection of meconic acid in the above manner of course proves the presence of opium in the tincture. When this information alone is sought, the paregoric may be diluted in a test-tube with proof-spirit till it is of a light yellow colour, and a drop or two of solution of ferric chloride then added. If opium be present, more or less deep red coloration will be produced, owing to the formation of meconate of iron. By comparing the depth of red colour with that given by a standard tincture, a rough indication of the proportion of opium present can be obtained; but the amount of meconic acid in opium is too variable to allow of much

[1] Where a more exact determination is required, it may be made by the method described in Volume I., under the head of Tinctures.

[2] The author has occasionally observed the benzoic acid thus extracted to have a distinct urinous odour.

stress being placed on the result obtained. It sometimes happens that paregoric is coloured with cochineal or contains a variety of tannin, in which case the coloration with ferric chloride becomes obscured. On cautiously adding hydrochloric acid, drop by drop, the colour produced by tannate of iron is destroyed, while that due to the meconate persists till considerably more acid has been added.

The proportion of opium in paregoric is too small to allow of the ordinary method of determining morphine being conveniently used; but fair results, sufficiently accurate for most purposes, may be obtained by volumetric or colorimetric application of the reactions with potassium ferricyanide and iodic acid (pages 317, 318).

Toxicology of Opium and Morphine.

In whatever form or manner it may be administered, opium is found to act as a typical and powerful narcotic, and in excessive doses is fatally poisonous.[1]

[1] In a letter to the *Globe*, Dr Wm. Moore, late Surgeon-General, Bombay, points out the exaggerated statements made respecting the ill effects of opium eating and smoking. He writes:—"No one denies that the excessive use of opium—whether smoked, eaten, or drunk—produces injurious consequences; but so does excess in the use of spirits, of roast goose, or even of fruit. . . . . . I am quite sure that the use of opium, speaking generally, is more advantageous than deleterious. Anti-opiumists assert that all using the drug in any form go from bad to worse, and eventually succumb to the effects. This is not the fact. There are thousands who use opium moderately from their youth upwards, and never suffer therefrom. That the habit cannot be given up is also incorrect. But, as a matter of fact, immoderate consumers are like drink-cravers, and rarely give up the habit. And moderate consumers do not do so, finding that it does not work them harm.

" . . . . . The use of opium, even in excess, is neither so deleterious to the consumer nor so dangerous to his neighbours as the use of spirits to excess. The opium eater or smoker . . . . . attains to a placid repose, which is very different to the excitement caused by spirits. . . . . . Many maladies for which opium is used in the East have been attributed to opium. Numbers of people suffering from all kinds of maladies are to be found in Eastern opium-houses. But the people thus affected fly to opium for a relief to suffering, and visitors finding diseased people in the opium-houses have ignorantly attributed the maladies seen to the use of opium. . . . . . Opium prevents eremacausis or waste of tissue, and thus contributes to endurance of fatigue, as evidenced by the long distances Kossids travel in India, their only support being a small pill of opium, a number of which they carry in a tin box. This is evidenced also by opium being given to camels, in combination with other substances, when these animals are called upon for extraordinary exertions. Opium also enables persons to live on smaller quantities of food than they could otherwise do—in this respect it resembles tea. Thousands were kept alive during Indian famines who would have succumbed from want of food had not opium been available. . . . . . There is also no doubt that opium exerts a prophylactic

The poisonous effects of opium are essentially due to the morphine contained in it, and the symptoms it produces differ but little from those consequent on the administration of pure morphine, except that there is a greater tendency to convulsions, and in the latter case the effects are usually manifested more rapidly than in the former, generally commencing in from five to twenty minutes if the poison has been taken in solution.

After poisoning by morphine or opium, dimness of sight and relaxation of the muscles, with drowsiness and stupor, are usually the first symptoms observed. At first the patient may be aroused without much difficulty, but as time goes on this becomes impossible, the drowsiness passing into complete coma, often accompanied by slow and stertorous breathing, ending in death. In the large majority of cases the pupils are strongly contracted in the earlier stages; but later, and when a fatal termination is approaching, they are often dilated.[1] They are usually insensible to light. Occasionally, especially with excessive doses of opium, there is vomiting, or even purging. The pulse is at first weak, quick, and irregular, but afterwards slow and full.

Poisoning by morphine or opium often closely simulates alcoholic drunkenness, and, in the absence of a smell of opium in the breath or vomit, it is often very difficult to distinguish between them. Other diseases, notably uræmic poisoning due to rupture of the bladder, are apt to be mistaken for poisoning by morphia.

The dose of morphine necessary to destroy life is extremely variable. Infants and young persons are peculiarly susceptible to opium and its preparations. Death has been caused to infants by

effect against malarious fevers, which effect is recognised, not only in the East, but also in the aguish districts of this country. That it relieves chronic painful maladies does not require proof.

" . . . . . People in the East will have opium—for with them it takes the place of other stimulants or narcotics—and they will have it in spite of anything anti-opiumists may advance to the contrary. . . . . . In opium they have a cheap, easily carried stimulant or narcotic, according as they may use it, and nothing the anti-opiumists may say will prevent the use of opium. Eating opium is more deleterious than smoking the drug, for it interferes more with the digestive capacities. Taking opium in the form of opium water (*umal pawnee*) is less injurious. Smoking opium is the least harmful manner of using the drug. It is not opium that is used for smoking, but a preparation of opium called *chandul* or *chandoo;* and, after much experience and investigation, I regard smoking *chandul* as harmless, unless indulged in to excess. And the vast majority of those using *chandul* do not, like the vast majority of those using spirits, proceed to excess.—15 Portland Place, March 10, 1891."

[1] A. Swaine Taylor mentions a case of opium poisoning in which one pupil was contracted and the other dilated.

$\frac{1}{8}$th, $\frac{1}{10}$th, $\frac{1}{15}$th, and even $\frac{1}{18}$th of a grain of opium; as also by a few drops, and even a single drop, of tincture of opium. On the other hand, children have recovered after doses of 1 grain, 5 grains, and 7½ grains of opium, and after two teaspoonfuls of laudanum. Half a grain of morphine acetate has proved fatal to an adult; but as a rule, the usual minimum fatal dose for an adult may be stated as 1 grain of a salt of morphine, or 7 grains of opium. Personal habit, as in the case of opium-eaters, and idiosyncrasy will of course largely modify the above conclusion.

The *post-mortem* appearances of poisoning by morphine are by no means well-marked. The stomach and intestines usually appear healthy. If opium itself has been taken, its peculiar and characteristic odour may often be recognised when the stomach is first opened.[1] Congestion of the lungs and brain are most commonly met with; but these appearances are not invariable, and when they exist, afford no definite evidence of opium poisoning. The blood is usually very fluid.

Besides opium itself, morphine and its salts, and the various official preparations of opium (*e.g.*, the tincture and extract), there are various nostrums containing opium, which have not unfrequently been the cause of death; especially in the case of infants, for whom opiates may be regarded as generally dangerous and unsuitable.[2]

[1] The author has observed an unmistakable smell of opium in the contents of the bladder sixty hours after death by taking laudanum.

[2] *Syrup of Poppies* is professedly a sweetened decoction of English or white poppy heads. It is of very variable strength, and is said to be sometimes substituted by a mixture of tincture or infusion of opium with simple syrup.

Winslow's Soothing Syrup sometimes produces symptoms of narcotic poisoning. It is said to contain about 1 grain of morphine and other opium alkaloids in an ounce (*Pharm. Jour.*, [3], ii. 975).

Godfrey's Cordial is stated to be a mixture of treacle and sassafras with 1 drachm of tincture of opium in 6 ounces. Half a teaspoonful is said to have caused the death of an infant; and in the years 1863–67, fifty-six deaths were recorded from its use, probably by its administration in excessive doses by ignorant persons.

Hawksworth's Mixture contains magnesium carbonate, rhubarb, compound spirits of ammonia, sweet spirit of nitre, oil of cassia, simple syrup, water, and other ingredients, with 1 part of tincture of opium in 54.

Chlorodyne is a preparation of variable character, containing chloroform, ether, alcohol, oil of peppermint, hydrocyanic acid, treacle, and morphine hydrochloride. Lobelia, capsicum, belladonna, and extract of liquorice are sometimes added.

Paregoric Elixir is the popular name for the compound tincture of camphor, B.P. Various preparations, destitute of opium, are sold as "paregoric substitute," &c., and if not dangerous in themselves, accustom ignorant persons to give and take large doses, which when repeated with genuine paregoric cause dangerous and even fatal effects.

DETECTION OF MORPHINE AND OPIUM.—In cases of suspected poisoning the detection of opium is based, in addition to the recognition of its smell, on the extraction of morphia and meconic acid in a sufficiently pure form to allow of the production of their characteristic reactions. The following is the usual mode of procedure :—

Observe if any smell of opium is apparent. If not, it may become evident on gently warming some of the contents of the stomach. Test a small quantity of the strained or filtered liquid with ferric chloride, and note if any red coloration (characteristic of meconic acid) is produced.

Next cut up the stomach and any solid contents into small pieces, and reduce the whole to pulp by beating in a mortar. Mix the product with the liquid contents of the stomach, and treat the whole with rectified spirit acidulated with acetic acid, in sufficient quantity to coagulate the albumin.[1] Keep the mixture warm for some time, with occasional agitation. Then filter or strain from the solid matter.

The filtrate is treated with basic acetate of lead as long as a precipitate is produced, when the liquid is boiled and allowed to cool. When cold it is again filtered, and the precipitate washed with cold water. The precipitate contains the meconic acid of any opium present. It should be washed off the filter with water, and completely decomposed by passing a rapid stream of sulphuretted hydrogen gas. The liquid is next filtered, and concentrated to a small bulk by evaporation at as low a temperature as possible. It should then be placed in a porcelain dish and tested with ferric chloride, which will produce a purplish red coloration if meconic acid be present. It is necessary to distinguish carefully between the coloration produced by meconic acid and the somewhat similar reactions given by thiocyanates and acetates. This may be effected with certainty as described on page 338.

A very useful indication of the amount of opium present may be obtained by comparing the depth of tint produced by ferric chloride with that obtained on treating a known quantity of opium in a similar way.

The filtrate from the lead precipitate will contain any morphine which may have been present. Separate the excess of lead by passing sulphuretted hydrogen for some time, filter, evaporate cautiously nearly to dryness, add a little water and filter. The filtrate will probably have a bitter taste if morphine (or other

[1] Meconic acid adheres very tenaciously to albuminous matters, and hence the precipitate should be digested with strong alcohol, and the liquid strained and added to the main solution.

alkaloid) be present. Transfer the solution to a stoppered separator, render the liquid alkaline with ammonia or (preferably) an alkaline bicarbonate, and shake with hot amylic alcohol without delay, as described on page 316. The amylic alcohol solution is then separated, passed through a dry filter, and either at once evaporated to dryness, and the residue examined by the colour-tests described on page 313 *et seq.*, or it is shaken with a little dilute hydrochloric acid, which is then separated and examined for morphine. An estimate of the quantity of morphine present may be obtained from the intensity of colour produced by the iodic acid and ferricyanide tests (page 318).

Instead of treating the alcoholic extract of the material under examination with basic acetate of lead, as described in the foregoing process, the method may in some cases be shortened and rendered more delicate by evaporating off the alcohol at a low temperature, taking up the residue with water, filtering, acidulating the filtrate with dilute sulphuric or hydrochloric acid, and agitating with ether.[1] This removes meconic acid, though not perfectly, while phosphates and other interfering matters remain in the aqueous liquid, and if the ethereal layer be separated, evaporated, and the residue treated with hot water, a solution is obtained, which after filtration may be very advantageously used for the application of the ferric chloride test. If preferred, the solution may be treated with lead acetate, and the meconic acid recovered from the filtered and washed precipitate by decomposing it with sulphuretted hydrogen.

The positive detection of meconic acid affords as perfect a proof of the presence of opium as does the recognition of morphine itself; and as the tests for and methods of separating meconic acid from foreign matters are somewhat more satisfactory than those for morphine, and the acid is more stable than the alkaloid, it occasionally happens that the acid may be isolated and positively identified, when morphine cannot be recognised with certainty (especially where ptomaines may be present).[2] The detection of meconic acid of course indicates the pre-existence of actual opium or some galenical preparation thereof, and not morphine or one of its salts. Hence it sometimes enables a useful distinction to be drawn as to the form in which the poison was taken.

[1] After this treatment the aqueous liquid may be rendered alkaline with sodium bicarbonate, and agitated with hot amylic alcohol for the extraction of the morphine.

[2] The author obtained satisfactory proof of the presence of meconic acid in the stomachs of two children exhumed five months after death, whereas no positive conclusion could be formed as to the presence of morphine.

It not unfrequently happens, even in cases in which it is certain that opium was the cause of death, that no trace of morphia or meconic acid can be found on analysis of the stomach or its contents. In other cases the poison has been detected with moderate facility a considerable time after death. The cause of these discrepant results is very obscure, but they are probably mainly dependent on the opportunities which circumstances have given for the elimination or absorption of the poison before death has ensued. Hence the failure to find morphine does not prove that its administration was not the cause of death. Attempts to extract morphine from the blood and tissues have usually failed, but T. G. Wormley has succeeded in isolating it from the brain, blood, liver, and urine of animals poisoned by it (*Chem. News*, lxii. 79, 99).

In examining urine for morphine, a considerable quantity of urea is liable to be taken up by the amylic alcohol. If the solution in this menstruum be evaporated and treated with cold water, a notable quantity of morphine is dissolved together with the urea. In the minute quantity present it may be extracted from the liquid by ether (which does not dissolve urea), or preferably by a mixture of ether and acetic ether.

STRYCHNOS ALKALOIDS.

The various species of *Strychnos*, a genus of plants belonging to the order *Loganiaceæ*, contain certain alkaloids remarkable for their intensely poisonous properties. Of these, the only two which have been thoroughly investigated are strychnine and brucine, the latter base being probably a dimethoxy-strychnine.

Strychnine and brucine occur in the seeds of the *Strychnos nux vomica*, in combination with lactic and igasuric acids. A third base, igasurine, has been supposed to exist in nux vomica; but the researches of W. A. Shenstone (*Jour. Chem. Soc.*, xxxix. 453) have proved the supposed alkaloid to be merely a mixture of strychnine and brucine. The bark of *Strychnos nux vomica* is also very poisonous, and is sometimes termed "false angustura bark." The extreme bitterness of the strychnos bark, its twisted appearance, the impossibility of separating it into thin layers, and the blood-red coloration produced on applying nitric acid to the internal coat, are characters by which it is easy to distinguish it from true angustura bark.

The seeds of *Strychnos Ignatiæ*, commonly called "St Ignatius' beans," also contain strychnine and brucine, and

are employed for the manufacture of the alkaloids, of which they are said to contain from 1½ to 2 per cent.[3]

The *leaves* of *Strychnos nux vomica* are said to contain brucine but no strychnine.[1]

The decoction of the root-bark of *Strychnos Tieuté* or "deadly upas tree" of Java, evaporated to an extract, is the chief ingredient of the arrow-poison *upas-tieute*. It contains strychnine and brucine.[1]

The deadly effects of *Curare* or Indian arrow-poison have been attributed to strychnine, but are now proved to be due to a distinct base, curarine, which is described on page 388.

Strychnine. Strychnia. $C_{21}H_{22}N_2O_2$.[2]

Strychnine exists, together with brucine, in the seeds and bark of *Strychnos nux vomica*, in the seeds of *S. Ignatiæ*, called "St Ignatius' beans," and in certain other plants of the same genus.[1] It may be prepared from these sources by a method similar to that used for their assay (page 385).[3]

Strychnine occurs as a white powder, or in crystalline particles of variable appearance. The crystals are sometimes minute pearly

[1] Strychnine appears to have been found with certainty in five or six species of *Strychnos* only. Several of the genus contain neither strychnine nor brucine.

[2] According to Claus and Glassner (*Ber.*, xiv. 778) the strychnine of commerce has not always the same composition, being represented in some instances by the formula $C_{22}H_{22}N_2O_2$, and in others by $C_{21}H_{22}N_2O_2$. They believe the plant produces the alkaloid with a variable proportion of carbon, a supposition which has also been entertained by Schützenberger. Koefoed, by fractional precipitation of commercial strychnine with potassium platinosochloride, obtained at first a salt containing 18·8 per cent. of Pt, corresponding to a molecular weight of 347·6 for the alkaloid, while the precipitate subsequently thrown down contained 19·35 per cent. of platinum, representing a molecular weight of 333·2, against 333·3 required for the formula $C_{21}H_{22}N_2O_2$. Hence commercial styrchnine probably contains homostrychnine, $C_{22}H_{24}N_2O_2$, in addition to the base of recognised composition.

[3] Nux vomica seeds or St Ignatius' beans are boiled with dilute sulphuric acid till soft, then crushed, and the expressed liquid treated with slaked lime in excess. The precipitate is filtered off and boiled with alcohol of 0·85 specific gravity, which dissolves the alkaloids and deposits the strychnine on cooling, the brucine mostly remaining in solution. The *British Pharmacopœia* directs that the powdered seeds shall be exhausted with dilute alcohol, the spirit distilled off, and the solution precipitated with acetate of lead. From the filtrate the alkaloids are precipitated with ammonia, and redissolved in boiling rectified spirit, the greater part of which is then distilled off. The residual liquid on cooling deposits the strychnine, which is washed with a mixture of 2 parts of rectified spirit and 1 of water till the washings cease to become red on adding nitric acid, indicating freedom from brucine. It is then recrystallised from boiling alcohol.

scales, like mica; sometimes octahedra, with a rhombic base; but more commonly form large, four-sided prisms. The crystals vary much according to the solvent from which they are deposited. For their production on a microscopic scale it is best to let the alkaloid deposit gradually by addition of an alkali to the solution of one of its salts; or to expose the solution to ammoniacal vapours (see page 364). Well-formed crystals of strychnine are also obtained by gradually adding water to the alcoholic solution of the free base.

Crystallised strychnine has an approximate specific gravity of 1·13 (T. P. Blunt).

Strychnine has no smell and is not deliquescent. On being heated it melts without decomposition at 265°–266° C., and sublimes imperfectly. Its solutions exert a lævo-rotatory action on polarised light, have a marked alkaline reaction, and are extremely bitter.[1]

Strychnine is an exceedingly violent tetanic poison (page 372).

Strychnine is very sparingly soluble in cold water, requiring about 8300 parts for its solution, but it dissolves in 2500 parts of boiling water. It requires 207 parts of cold absolute alcohol for solution, and about 400 of whisky, 500 of spirit of ·941 sp. gravity, and 2617 parts of ·970 sp. gravity. The limited solubility of strychnine in alcohol is utilised for its separation from brucine, which is readily soluble in the same liquid. Strychnine is soluble in 8 to 10 parts of chloroform, but dissolves very sparingly in ether, requiring 1400 parts of the anhydrous menstruum, or about 1050 of ordinary commercial ether. Doubtless the physical condition of the alkaloid largely affects its solubility. Strychnine dissolves with facility in a mixture of equal measures of chloroform and ether—a fact often utilised for its extraction. It is soluble also in 140 parts of benzene, and is deposited on spontaneous evaporation in large brilliant octahedral crystals. In petroleum ether strychnine is nearly insoluble, requiring, according to Wormley, about 12,500 parts for solution.

Strychnine is not removed from its acidulated solutions by agitation with any of the above immiscible solvents, but, on the contrary, may be completely extracted from its solutions in them by shaking the liquid with dilute sulphuric acid.

Strychnine is not sensibly soluble in solutions of the fixed caustic alkalies, but dissolves somewhat more readily in ammonia. In dilute acids it is readily soluble.

[1] The bitterness of strychnine is said to be recognisable in a solution of $\frac{1}{10}$th of a grain per gallon. The salts of strychnine are much less bitter than the free alkaloid.

Strychnine dissolves without coloration in the strong mineral acids. It may be heated to 100° C. with strong sulphuric acid without visible change, and is often stated to be unaltered by such treatment. But the strychnine cannot be wholly recovered from the product, and C. Stoehr (*Ber.*, xviii. 3429) has shown that a sulphonic acid is formed.[1]

Monobromstrychnine, $C_{21}H_{21}BrN_2O_2$, is obtained on adding bromine-water in theoretical quantity to an aqueous solution of strychnine hydrobromide or hydrochloride, and then precipitating with ammonia. The aqueous solution is alkaline and very bitter (*Arch. Pharm.*, ccxxviii. 313).

SALTS OF STRYCHNINE.

Strychnine is a strong base, and forms salts which are usually crystallisable and soluble in water, yielding very bitter, exceedingly poisonous solutions. The salts of strychnine are mostly soluble in alcohol, but are insoluble in ether, chloroform, benzene, petroleum spirit, or amylic alcohol.

Strychnine may be titrated with accuracy by a standard mineral acid, using litmus or methyl-orange as an indicator. One c.c. of decinormal acid corresponds to 0·0334 gramme of strychnine. Strychnine has no effect on phenolphthaleïn, and hence its salts react with this indicator as if the acids were uncombined.

The *chromate*, *ferrocyanide*, *mercurochloride*, *phosphotungstate*, and *phosphomolybdate* are among the most insoluble salts of strychnine. All these forms are occasionally used for the isolation or estimation of the alkaloid. The high insolubility of the ferrocyanide serves to separate the alkaloid from brucine.

The sparing solubility of the hydriodide of strychnine is important, as the salt is liable to be thrown down in the form of crystalline needles from mixtures in which strychnine hydrochloride and a metallic iodide are dispensed together. The hydrobromide is stated to be similarly liable to separate out.

None of the salts of strychnine find any place in the *British Pharmacopœia*. The *sulphate* is official in the United States, and the *nitrate* in Germany. The following table indicates the leading characters of the principal salts of strychnine.

[1] STRYCHNINE-MONOSULPHONIC ACID, $C_{21}H_{21}N_2O_2.SO_3H$, is produced in nearly theoretical amount when strychnine is heated to 100° with the requisite quantity of concentrated sulphuric acid. The free acid is colourless, and very little soluble in water or alcohol. The ammonium salt is very soluble in water, but precipitated by alcohol; and the potassium, sodium, barium, calcium, lead, and copper salts form very insoluble precipitates. With fuming sulphuric acid at 150° a soluble *disulphonic acid* is formed.

Salt.	Formula.	Appearance.	Proportion of Strychnine.	Solubility.	
				Cold Water.	Boiling Water.
Hydrochloride,	BHCl	Silky needles.	84 per cent.	1 part in 50	...
Hydrobromide,	BHBr	Prismatic needles.	80 „	„ 82	...
Hydriodide, .	BHI	Quadrangular needles, or white scales.	72·3 „	Sparingly.	—
Nitrate, . .	$BHNO_3$	Silky needles.	84 „	1 part in 90	1 part in 3
Sulphate, .	$B_2H_2SO_4$+ 6 aqua (or 5 aqua)	Transparent quadratic octahedra.	75·4 „	„ 42	„ 2
Acid sulphate,	BH_2SO_4+ 2 aqua	Long, thin needles.	71·4 „	...	...
Acetate, . .	...	Crystallises with difficulty.	...	1 part in 96	...

Analytical Reactions of Strychnine.

1. On adding to a not too dilute solution of a soluble salt of strychnine a fixed caustic alkali, alkaline carbonate, ammonia, or lime-water, strychnine is thrown down as a white precipitate insoluble in excess of the precipitant. The precipitate rapidly becomes crystalline. The crystals have a characteristic microscopic appearance, being usually long, rectangular, well-defined prisms. They are well developed if a drop of a dilute solution of a strychnine salt (*e.g.*, the acetate or sulphate) be placed on a slip of glass, and covered with a small beaker rinsed with strong ammonia. After half an hour the beaker may be removed, the drop of liquid covered with a circle of thin glass, and examined under the microscope. If the solution contain extraneous matter, it may be found difficult or impossible to obtain crystals from it.

2. If strychnine be liberated from the solution of one of its salts by one of the reagents mentioned above, and the liquid (with the suspended precipitate) be *at once* shaken with an equal measure of chloroform, the alkaloid is readily dissolved by the latter liquid, and may be obtained in a solid state by separating the chloroform and evaporating it to dryness at a steam heat. The agitation of the aqueous liquid with chloroform should be repeated if quantitative results are desired. From aqueous liquids containing little solid matter, chloroform separates tolerably readily, but if, as often happens in practice, there be much extractive matter present, the complete separation of the chloroform requires many hours or even days. This inconvenience may be wholly avoided by substituting for pure chloroform a mixture of equal volumes of ether and chloroform. This has a density of 1·11, and separates with facility from aqueous liquids (compare pages 156 and 374). Experiments

by the author have shown that the solubility of strychnine in a mixture of equal measures of chloroform and ether is amply sufficient to ensure its separation from the aqueous liquid (*Analyst*, vi. 141).

3. A very useful precipitant for strychnine in complex organic liquids is a nitric acid solution of sodium phosphomolybdate (Sonnenschein's reagent, page 136). On adding this to a neutral or slightly acid solution of the alkaloid, the strychnine is thrown down as a yellowish white amorphous precipitate. The *separation is complete even in very dilute liquids*. *Many alkaloids* besides strychnine give similar precipitates, and hence the reagent is merely of service for concentrating the strychnine and purifying it from extraneous matters. The precipitate should be filtered off, washed with water containing the reagent, and the strychnine separated by suspending the precipitate in water, adding ammonia, and agitating with ether-chloroform, as in test 2. The precipitate can, however, be directly examined by the colour-reactions described on page 368.

4. Scheibler's reagent (page 136) precipitates strychnine from extremely dilute solution, and may be substituted (with advantage) for the phosphomolybdic reagent.

5. *Strychnine may also be separated from its tolerably* concentrated neutral solutions by precipitation with chromate of potassium. The test is best applied to a chloroform-residue obtained as described in 2. This should be dissolved in dilute acetic acid, the liquid filtered, if necessary, and evaporated to dryness at 100°. The resultant acetate of strychnine is dissolved in a little cold water, and neutral chromate of potassium is added to the solution. Strychnine chromate, $(C_{21}H_{22}N_2O_2)_2,H_2CrO_4$, is thrown down as a reddish or yellowish brown precipitate, soluble in boiling water (1 in 171) and re-deposited on cooling in orange- or lemon-yellow needles and plates. The precipitate is very slightly soluble in cold water (1 in 470), a fact which enables strychnine to be separated from brucine, the chromate of which is more soluble. Potassium bichromate throws down from solutions of strychnine, not too dilute, an anhydrochromate of the formula $B_2H_2Cr_2O_7$ as a crystalline precipitate, in which octahedra and bush-like groups are the most prominent microscopic forms. The precipitate is not soluble in excess of the reagent or in very dilute acids, and its formation is much facilitated by stirring. It dissolves in 1800 parts of cold and about 240 parts of boiling water, and is rapidly affected by exposure to light. The chromates of strychnine give the characteristic violet oxidation-product directly on treatment with strong sulphuric acid as described in paragraph 8; or the alkaloid may be obtained in a free state by suspending the pre-

cipitate in water, adding ammonia, and agitating with ether-chloroform, as in 2.

6. With iodised potassium iodide strychnine gives a reddish-brown precipitate, even in extremely dilute solutions (1 : 100,000). Mayer's reagent also precipitates strychnine from very dilute solutions (1 : 150,000), and is recommended by G. F. Schacht for its determination.

7. Strychnine forms a combination with iodine analogous to, and having similar optical properties with, herepathite. The following is the best method of utilising the reaction for the detection of strychnine. On a microscope-slide place a very small drop of an alcoholic solution of iodine, and allow it to evaporate. *Directly* it is dry add a drop of a solution of strychnine, made by dissolving the alkaloid in dilute acetic acid and adding a drop of sulphuric acid. Add also a drop of rectified spirit, and allow the mixture to evaporate spontaneously. On examining the residue under the microscope with a Nicol's prism and selenite, but using no analyser, characteristic crystalline structures will be observed. These may take the form of small circular tufts of very fine black needles; of minute dots of a more or less triangular form, exhibiting yellow, pink, and green tints; large triangular crystals of a yellow or green colour, composed of three parts radiating from a centre; numerous solid macled prisms, occasionally showing complementary tints; or solid rosettes of four, five, and six sided prisms. In all cases it is desirable to compare the results with those obtained from a minute quantity of strychnine treated in precisely the same manner. The mode of operation may be varied considerably, provided that the essential conditions of simultaneous presence of alcohol, sulphuric acid, acetic acid, free iodine, and a trace of strychnine be duly observed. The test is said to be sensitive to 1–2500 of a grain of strychnine.

8. When potassium ferrocyanide is added to the solution of a salt of strychnine, the ferrocyanide of the base, $B_4H_4FeCy_6+4H_2O$, is precipitated as a white crystalline powder with a shade of yellow, only very sparingly soluble in cold water. The observation, which is due to Beckurts, has been utilised by Dunstan and Short (*Year-Book Pharm.*, 1883, page 469) for the determination of strychnine and its separation from brucine, the ferrocyanide of which is readily soluble. A quantity, not exceeding 0·2 gramme, of the mixed alkaloids is dissolved in about 10 c.c. of water containing 5 per cent. by measure of strong sulphuric acid, the solution diluted with water to about 175 c.c., and then made up to 200 c.c., with a 5 per cent. aqueous solution of potassium ferrocyanide. The liquid is stirred occasionally during

six hours, and is then filtered off and washed with water acidulated with $\frac{1}{40}$ of sulphuric acid, till the washings are free from bitterness. As the precipitate is liable to alteration on drying,[1] it should be washed off the filter with strong ammonia and extracted by agitation with chloroform. After separating the chloroform solution and washing it with water, the strychnine may be titrated by standard acid and methyl-orange, or the chloroform may be evaporated to dryness and the residual alkaloid weighed. Some alcohol should be added towards the end of the evaporation to prevent the violent decrepitation which otherwise ensues.[2] From the filtrate from the ferrocyanide precipitate the brucine may be precipitated by ammonia and extracted by chloroform. Schweissinger (*Archiv des Pharm.*, [3], xii. 579, 609) states that he had not found the ferrocyanide method to effect a perfect separation of strychnine and brucine. He found strychnine ferrocyanide to be perfectly insoluble in water acidulated with sulphuric acid, but the brucine salt was not completely soluble, and was precipitated more or less perfectly after a time. Hence the strychnine was always estimated too high and the brucine too low, the error largely depending on the time allowed and the concentration of the liquid.

When the precipitation of the strychnine as ferrocyanide is effected in a liquid strongly acid with hydrochloric acid, the salt thrown down is insoluble in cold water and alcohol, has a bluish shade, and is an acid ferrocyanide containing B,H_4FeCy_6. No similar precipitate is obtained with brucine except in highly concentrated solutions, or after long standing. Holst and Beckurts (*Arch. Pharm.*, [3], xxv. 313) have based on this fact the following volumetric method of determining strychnine. A 1 per cent. solution of the alkaloids is strongly acidulated with hydrochloric acid, and a standard solution of potassium ferrocyanide solution added until a filtered portion of the liquid gives a blue stain with paper moistened with ferric chloride. 224 parts of ferrocyanide represent 334 of strychnine. The following results were obtained:—

	Strychnine.		Brucine.	
	taken.	found.	taken.	found.
No. 1, . .	0·145 grm.	0·148 grm.	0·036 grm.	...
No. 2, . .	0·100 ,,	0·1017 ,,	0·050 ,,	0·04915 grm.

[1] According to Beckurts, upon exposure to air strychnine ferrocyanide turns yellow, and is eventually completely decomposed with formation of strychnine ferrocyanide and a new base which can be extracted with alcohol, called oxystrychnine, $C_{21}H_{22}N_2O_3$.

[2] Dunstan and Short state that this behaviour is characteristic of pure strychnine, a minute admixture of brucine preventing it and causing the alkaloid to have a fused appearance.

9. On treating a *cold* solution of strychnine in concentrated sulphuric acid with an oxidising agent of almost any kind, a rich purple-blue coloration is developed. This changes more or less rapidly through purple and crimson to a bright cherry-red tint, which is somewhat persistent. The rapidity of the change of colour is largely dependent on the nature and quantity of the oxidising agent employed. Various substances have been recommended for the purpose. The following are the most notable :—

(*a*) *Potassium bichromate.* This is a favourite oxidising agent with many operators, but in the experience of the author is one of the least reliable reagents for the purpose, as the change of colour is very rapid and the green chromium compound resulting from the reaction tends to mark the coloration due to the strychnine.

A useful way of employing bichromate is to precipitate the strychnine by means of it (as in 5), and apply sulphuric acid to the precipitate. This plan has the great advantage of separating brucine, the presence of which is objectionable.

(*b*) *Potassium permanganate,* originally recommended by Guy, gives the reaction with great distinctness, but the rotation of tints is very rapid, and the reagent itself is apt to give a crimson colour with sulphuric acid.

(*c*) *Potassium ferricyanide,* a reagent proposed by E. Davy, gives exceedingly good results. The change from blue to crimson and red is very rapid.

(*d*) *Lead dioxide* (PbO_2). This oxidising agent, suggested by Marchand, acts remarkably well, but the puce colour natural to it is apt to distract the attention from the reaction to be looked for.

(*e*) *Manganese dioxide* (MnO_2). This reagent, originally recommended by Mack, employed in moderate quantity and in the finally powdered state, is the one to which the author gives preference. The play of colours is remarkably well-developed, and the change of tint very gradual.

P. R. Mandelin recommends a solution of 1 gramme of *ammonium vanadate* in 100 c.c. of sulphuric acid as a reagent which will keep unchanged, and which gives the colour-reaction with great distinctness.

(*f*) *Cerosoceric oxide* (Ce_8O_4) has been highly recommended as the oxidising agent by S. D. Hinsdale. It has the advantage of being light in colour, and giving a colourless reduction-product.

The oxidation-test for strychnine is usually performed in practice

on the residues left by evaporating to dryness the ether-chloroform with which an alkaline solution of the alkaloid has been agitated. The test may, however, be directly applied to the chromate or phosphomolybdate of strychnine (see reactions 4 and 5). The following mode of operating is best calculated to ensure delicacy and accuracy :—

The solution of the strychnine in ether-chloroform should be evaporated in a porcelain dish or crucible. If the quantity of strychnine to be sought for is likely to be very small, the dish should be immersed in hot water, and the solution of the alkaloid allowed to fall slowly into it from a burette or pipette, so that each drop may almost completely evaporate before another arrives. In this manner the strychnine-residue may readily be confined to a very small area, and the after-reactions thus rendered proportionately delicate. When quite dry and cold the residue should be treated with two or three drops of pure concentrated sulphuric acid, which should be thoroughly incorporated with it by means of a glass rod. The mixture should then be allowed to stand for five minutes in order to note if any colour is produced. Salicin and certain other bodies will cause a red coloration, while some may be more or less charred. If any marked coloration is produced, the dish should be gently heated (not to the boiling-point of water) for half an hour, the contents diluted with water, filtered, made alkaline with ammonia, agitated with a mixture of ether and chloroform (as in test 2), and the strychnine recovered by evaporating the solvent. The residue is then again treated with a drop or two of sulphuric acid.

The oxidising agent, which should be, by preference, manganese or lead dioxide, is then added to the sulphuric acid by dipping a glass rod moistened with the latter into the powdered solid. A moderate quantity only should be used, so as not to obscure the reaction by excess of blackness. On stirring the drop of strychnine solution with the rod dipped in the oxide the blue coloration will become developed. In a minute or so it will be distinctly purple, passing in a few minutes to crimson, and ultimately to a cherry-red, the last tint being very persistent. The test is exceedingly satisfactory, delicate, and characteristic, but the order of colours is as important as their shades. The reaction is said to be capable of detecting $\frac{1}{20000}$th of a grain of strychnine.[1]

There are but very few substances which at all simulate the reaction of strychnine when treated with sulphuric acid and an

[1] The oxidation-reaction has been applied by Davies and Schmidt to the approximate determination of the strychnine in Easton's Syrup (*Year-Book Pharm.*, 1883, page 571).

oxidising agent, and few indeed of these that are dissolved together with strychnine on agitating the alkaline solution with ether-chloroform. Salicin, santonin, piperine, solanine, certain opium bases, cod-liver oil, and certain resins give colours with sulphuric acid alone, but they are extracted from acid solutions by ether and chloroform, and certain of them may also be got rid of by gently heating the liquid as already described. Aniline gives no colour with sulphuric acid alone, but coloured products are formed on treating the solution with an oxidising agent. These cannot be mistaken for the oxidation-products from strychnine, for the order of tints is entirely different, commencing, in the case of aniline, with a green, changing to a very persistent blue, and ultimately becoming black. Colocynth resin gives a very similar reaction to strychnine, but is readily extracted by agitating the acidulated solution with benzene or ether.

It is always *desirable* to purify the strychnine by extracting it from an alkaline liquid by agitation with ether-chloroform (see page 364), but the oxidation-reaction is readily obtained even in presence of considerable quantities of certain foreign matters. Thus oatmeal, tartar-emetic, and dextrin do not materially interfere with reaction when the quantity of strychnine is considerable. Some extractive matters, sugar, and nitrates wholly prevent the application of the colour-test, and hence the *absence* of strychnine must never be assumed *till* the test has been applied to an ether-chloroform residue.

Quinine, cinchonine, and veratrine may be found with strychnine in the ether-chloroform residue, but do not interfere with the application of the test. Morphine in small proportion does not interfere, and the presence of any larger quantity than traces is excluded by its limited solubility in the ether-chloroform.

In small proportions brucine exercises no injurious influence on the oxidation-test for strychnine, but when much is present it interferes in a marked manner. Hence it is safest to separate the strychnine first of all as chromate or ferrocyanide, as described in reactions 5 and 7, or a strong solution of a salt of the alkaloid can be treated with a very decided excess of ammonia, when the strychnine will be precipitated and the brucine will remain in solution. If a mixture of brucine and strychnine be treated with chlorine-water, the former base dissolves as dichlorobrucine, and the residue then gives the colour-reaction perfectly (Beckhurts). Brucine can be sought for in the filtrate, as described on page 383. In toxicological investigations its presence together with strychnine points to an administration of one of the natural sources of the alkaloids, rather than to the use of a purified

salt of strychnine. Commercial strychnine and its salts often contain traces of brucine, but not sufficient to interfere at all with the application of the oxidation-test.

Curarine, the active principle of the Indian arrow-poison, gives a series of coloured oxidation-products exactly like those of strychnine, but not being sensibly soluble in chloroform it is not liable to be found in the chloroform-residue (see page 389).

A ptomaine has been described by C. Amthor (*Chem. Zeit.*, xi. 228), which gives a blue colour with the oxidation-test less persistent and pure than that produced by strychnine. It is less bitter and less poisonous to frogs than strychnine, is dissolved readily by amylic alcohol but only slightly by ether from alkaline solutions, and gives an *amorphous* chromate, picrate, ferrocyanide, and ferricyanide. The formation of any such ptomaine must be very rare.

Many of the above sources of fallacy or confusion may be wholly avoided by performing the oxidation-test in a manner suggested by H. Letheby, which consists of employing electrolytic oxygen instead of either of the oxidising agents mentioned on page 368. The solution of the ether-chloroform residue in a drop or two of strong sulphuric acid is placed in a cup-shaped depression in a piece of *platinum foil. The foil is connected with the platinum plate of* a single Grove's cell, and a platinum wire connected with the zinc plate of the battery. Immediately that the end of this platinum wire is dipped into the drop of acid, the violet colour of the oxidation-product will flash out, and on removing the wire from the liquid the tint will remain.[1]

8. A colour-reaction of strychnine with chloride of zinc is described on page 145.

9. If solid strychnine be dissolved in a drop of dilute nitric acid, the liquid gently heated, and a minute particle of potassium chlorate then added to the warm liquid, an intense scarlet coloration is produced. This is changed to brown on adding ammonia, and on evaporation to dryness a dark green residue is left, soluble in water with green colour changed to orange-brown by caustic potash, and becoming green again on adding nitric acid. C. L. Bloxam, the observer of the foregoing series of colour-changes (*Chem. News*, lv. 155) did not obtain any corresponding reaction with the other alkaloids he tried.

10. A reagent prepared by adding sufficient strong hydrochloric acid to a weak solution of potassium chlorate to render it bright

[1] The reaction may be rendered still more delicate by placing the drop of liquid at the bottom of a porcelain crucible, and momentarily immersing in the liquid two platinum wires connected respectively with the zinc and platinum plates of the battery.

yellow, and then sufficient water to make it a very pale yellow, gives with a solution of strychnine in hydrochloric acid a fine red colour, destroyed by excess and restored by boiling. Brucine gives a violet coloration (C. L. Bloxam, *loc. cit.*).

11. An exceedingly delicate test for strychnine is the physiological one of Marshall Hall. A freshly-caught frog, the smaller the better, is the best subject for the experiment. The skin of the back should be raised with a pair of forceps, and a small slit made with a pair of scissors. Into the opening, the suspected liquid, as concentrated as possible, should be injected by means of a small pipette. The first symptom observed will be a difficulty in breathing, which gradually increases till the animal appears to gasp for breath. A slight tremor will be observed extending over the whole body, but specially noticeable in the hind legs. The frog sometimes remains perfectly quiet, but in other cases takes energetic and convulsive leaps. It should be placed under a beaker or bell-glass for easier observation. The characteristic tetanic convulsions next make their appearance. They are intermittent, the pupils being dilated during the spasms and contracted in the intervals. The convulsions may be induced by touching the frog, clapping the hands, or knocking on the table.

The physiological test is much reduced in practical value by the difficulty in obtaining young animals for experiment. On the whole it is decidedly less certain and characteristic than the chemical reactions, and in no case should be implicitly relied on unless confirmed by the results of the oxidation-test.

TOXICOLOGY OF STRYCHNINE.

Owing to the violently poisonous character of strychnine, and the ease with which its preparations (under the disguise of "vermin-killers," &c.) may be obtained by the public, cases of death from its effects are very numerous.[1]

The symptoms of poisoning by strychnine usually commence with a bitter taste, followed by a feeling of suffocation. The characteristic tetanic convulsions, often accompanied by opisthotonos, then come on, gradually becoming more frequent.[2] Vomiting is not common. Lockjaw is a constant symptom. Consciousness, as

[1] In the author's own experience of the examination of poisoned animals, extending over many years and to a great number of cases, strychnine has been found more frequently than all other kinds of poison taken together. He has met with it in several cases of murder of human beings, the criminals subsequently undergoing capital punishment, and in numerous cases of suicide and death by misadventure, including careless dispensing by a qualified medical man.

[2] Methyl-strychnine produces a paralysing effect more allied to that due to curare than to the tetanising effect of strychnine.

a rule, is retained till the last, accompanied by a lively terror of the rapidly-recurring and agonising fits. Death usually ensues within a few hours, but in rare cases life has been prolonged for several days. The general time is from thirty to ninety minutes.[1]

From $\frac{1}{12}$ to $\frac{1}{40}$ of a grain is the usual medicinal dose of strychnine, but it may be increased in the case of a person accustomed to it. One-sixth of a grain is usually distinctly dangerous. One grain may be regarded as the average fatal dose for an adult, and death has been known to occur from $\frac{1}{4}$ grain. Much larger doses have been recovered from.[2]

Hypodermic injections of strychnine have been very successfully employed as an antidote in cases of snake bite.[3]

The *post-mortem appearances* of poisoning by strychnine are not very striking or characteristic. Rigidity of the muscles is usually prolonged, but if death occur in one of the intervals between the fits, no rigidity will be observed. The heart is usually, but not always, full of blood, especially on the right side. The stomach usually appears normal, but sometimes intensely congested.[4] The

[1] In a case within the author's experience, in which medicine containing a poisonous dose of strychnine was taken, the victim, a young woman, immediately cried out that she was poisoned, and died in twelve minutes. Analysis of the remainder of the medicine showed the presence of rather more than one grain of strychnine in each dose, and the amount of poison recovered from the viscera agreed remarkably closely with this result.

[2] The most successful antidote for strychnine is the persistent inhalation of *chloroform* as often as the spasms come on. *Chloral hydrate*, in a dose of 30 grains, has proved highly efficacious on several occasions, in some instances the cramps being wholly prevented, while, on the other hand, no narcotic action of the antidote was manifested. Injection of *morphine* has proved similarly successful. *Tannin* and animal *charcoal* are of little value (*Year-Book Pharm.*, 1890, page 389). *Formyl-paraphenetidine* (page 85) has been recommended as an antidote for strychnine (*Pharm. Zeit.*, 1889, page 625).

[3] The strychnine is used as nitrate in 240 parts of water (= 2 grains to the ounce) mixed with a little glycerin. Twenty minims should be injected every 10 to 20 minutes until all the snake-poison symptoms have disappeared and slight muscular spasms are observed. A grain or more of strychnine may be required in the course of a few hours. Out of about one hundred cases treated in this way, some of them at the point of death, by Dr Mueller of Yackandandah, Victoria, there was only one failure, and that arose from the injections being discontinued after $1\frac{1}{4}$ grain of strychnine had been employed (*Pharm. Jour.*, [3], xxi. 1139).

[4] In a case in the author's experience, the stomach presented such an appearance as to suggest the presence of arsenic or other irritant poison; but no mineral poison could be detected. That death was due to administration of a vermin-killer containing strychnine was subsequently fully proved by analysis (and admitted by the murderer).

most characteristic appearance is the intense congestion of the brain and spinal cord, often accompanied with considerable effusion of blood.

For the *detection of strychnine* in the dead body, the following method should be used, the portions of the body operated upon being chosen according to the manner in which the poison is likely to have been administered. Thus it is of no use to search in the stomach or intestines for strychnine injected hypodermically. If the poison has undergone absorption, it will most probably be met with in the liver, but all parts supplied with blood and most of the secretions may contain small quantities of the poison. In extreme cases, it is desirable to operate on very considerable quantities of material, as death may be caused by so small a quantity of strychnine that the poison may be altogether missed if this precaution be not taken.

The portions of the body to be tested for strychnine should be cut into small fragments with a pair of scissors, and then further reduced by bruising in a mortar. The product is then treated with rectified spirit, mixed with about 1 part in 20 of acetic acid. This coagulates the albuminoids, while allowing of the complete solution of the strychnine. After a few hours the liquid should be strained through muslin, and the clarified filtrate passed through a paper filter. The clear liquid is next evaporated nearly to dryness, diluted with water, and again filtered. The filtrate is once more evaporated to dryness, and the residue thoroughly extracted with strong, and preferably absolute, alcohol. The liquid is filtered, the alcohol removed by evaporation, and a small quantity of water added. The solution is placed in a tapped separator, diluted to about 20 c.c. with water, and a few drops of hydrochloric or dilute sulphuric acid added. An equal measure of ether is next added, and the whole well shaken. On standing a few minutes, the ether will separate on the surface, when the aqueous liquid should be withdrawn through the tap, and the ether then run off into a separate vessel.[1] The aqueous liquid is then returned to the separator, and about 30 c.c. of a mixture of equal volumes of ether and chloroform added. Enough ammonia to render the liquid distinctly alkaline is next added, and then the whole *immediately* shaken thoroughly for about a minute. On coming to rest, the aqueous liquid will tend to separate from the mixed chloro-

[1] This preliminary treatment of the acidulated solution with ether is very important. It effects a separation of glucosides, traces of fat, essential oils, and other matters which otherwise would contaminate the strychnine. In some cases it is desirable to repeat the agitation with a mixture of equal measures of chloroform and ether.

form and ether, which has a density of about 1·1. If tolerably free from extractive matter, it will float on the surface of the ether-chloroform, but if largely charged with sugar or other soluble matter, it may be equally dense with the solvent, or even collect at the lower part of the separator. If, from the presence of extractive matters or for other reason, the liquids do not readily separate, water or ammonia should be added, so as to reduce the density of the aqueous liquid. An alternative, and perhaps preferable plan, is the gradual addition of ether, with cautious agitation, till the solvent separates readily at the surface of the aqueous liquid.[1]

When the division of the contents of the bulb into two layers is complete, the strata are separated from each other by means of the tap. If quantitative results are required, it may be desirable to agitate the aqueous liquid with a fresh quantity of ether-chloroform. The solution of the alkaloid in the ether-chloroform is passed through a small paper filter, if necessary, and then evaporated to dryness at a steam-heat in the manner described on page 369. The residue obtained may then be examined for strychnine by the tests given on page 364 *et seq.* If strychnine be present, the solution of the residue in alcohol will have a marked and persistent bitter taste, especially noticeable at the back of the tongue. The most delicate and characteristic chemical reaction of strychnine is the oxidation-test described on page 368. Reactions 5, 7, and 8, and the production of crystals of strychnine as described in 1, are also valuable as confirmatory tests, and should never be omitted if the material at disposal be sufficient for their performance. The bitter taste, however, in conjunction with a distinct reaction by the characteristic oxidation-test, may usually be regarded as ample proof of the presence of strychnine, provided the absence of interfering substances has been ensured by the previous treatment. The ptomaine, stated by C. Amthor (page 371) to give a colour-reaction simulating that of strychnine, can only be present when putrefaction has taken place, and its formation must be very rare, or it would have been met with in the numerous cases in which no alkaloidal substance has been detected.

Blood should be examined for strychnine by diluting it with an equal bulk of water, adding a little acetic acid, boiling for a

[1] This alternative is preferable to the addition of chloroform, which, if used in too large a proportion, will only separate from the dense aqueous liquid with extreme difficulty. The advantage of employing a mixture of ether and chloroform, rather than either solvent singly, has been pointed out by the author (*Analyst*, vi. 141), though its use did not originate with him.

short time, filtering, and evaporating the filtrate nearly to dryness. The residue is taken up with alcohol, and the solution treated as already described.

From urine, strychnine may be directly extracted by agitating the fluid with ammonia and ether-chloroform.

Dialysis through parchment-paper is an efficient and occasionally a convenient means of separating strychnine from organic matter. The finely-divided tissue should be suspended in water, to which some alcohol and acetic acid have been added. Distilled water should be used on the other side of the membrane, and changed at intervals of twelve hours. After thirty-six to forty-eight hours the dialysate may be evaporated to dryness, and treated with alcohol, &c., as described on page 374.

It has not unfrequently happened that a *post-mortem* analysis has failed to detect strychnine in corpses almost certainly containing it. This result has probably been due in most cases to the use of defective methods of analysis, or to the search being restricted to too small quantities of material or to wrong parts of the body. Occasionally, failure has probably been due to an elimination of the poison during life, especially in cases in which death has resulted from a minimum dose. Strychnine does not undergo decomposition in the dead body, and has been detected several years after death.[1] Hence, if elimination has not occurred prior to death, strychnine ought to be found by the toxicologist.

PREPARATIONS OF STRYCHNINE.

The only preparation of strychnine recognised in the *British Pharmacopœia* is a solution of the hydrochloride, which, as met with in commerce, is not so constant in strength as is desirable.

Easton's Syrup is a widely-used remedy, consisting of a syrup of the phosphates of iron, quinine, and strychnine. Its omission from the *British Pharmacopœia* is lamentable, and results in considerable variation in the composition of the preparations sold under its name. According to Squire (*Companion to the British Pharmacopœia*), when prepared according to Dr Easton's formula, the syrup contains "about 1 grain phosphate of iron, 1 grain phosphate of quinine, and $\frac{1}{32}$ grain phosphate of strychnine in each fluid drachm."

[1] The author has had no difficulty in detecting strychnine in a stomach preserved in spirit for six years. A portion of the untreated stomach and liver from the same person (who picked up in a field and ate an egg poisoned with strychnine) was kept in a jar, the mouth of which was closed by a bag containing wood-charcoal. On opening the jar after six years, the whole of the contents were found to have disappeared, with the exception of a small quantity of dust, in which abundance of strychnine was detected.

The following is the range of variation observed by Davies and Schmidt (*Year-Book Pharm.*, 1883, page 575) in ten samples of Easton's Syrup of commerce:—

	Squire's Formula.	B.P. Committee's Formula.	Found.			
			Highest.	Lowest.	Average.	
Quinine phosphate, $Qu_3(H_3PO_4)_2$,	6·87	6·0	7·83	1·57	5·09	Grains per fluid oz.
Ferrous phosphate, $Fe_3(PO_4)_2$,	5·30	8·0	12·32	0·97	6·91	,,
Free phosphoric acid,	38·03	50·0	49·24	19·36	34·38	,,
Strychnine, . . .	1·0	1·0	3·0	0·6	1·0 to 1·14	Grains per 4 fluid oz.
Specific gravity, . .	...	...	1·331	1·288	1·298	...

The following analyses of commercial Easton's syrup have been published by J. G. Wilson (*Pharm. Jour.*, [3], xix. 753):—

	A.	B.	C.	D.	E.	
Quinine phosphate, ...	5·75	5·75	5·25	4·25	2·00	Grains per fluid oz.
Ferrous phosphate, ...	7·1	7·5	6·4	5·0	5·0	
Phosphoric acid, ...	47·0	45·0	48·0	31·0	26·0	
Strychnine, ...	0·25	0·25	0·25	0·20	0·10	

In analysing Easton's syrup the *iron* may be determined by evaporating 5 c.c. of the preparation, igniting the residue, dissolving the ash in hydrochloric acid, and titrating the iron with standard bichromate solution after reducing it to the ferrous state.

The free *phosphoric acid* may be determined by titration of 10 c.c. with methyl-orange and semi-normal caustic soda. The neutral point is attained when NaH_2PO_4 is formed.

The *alkaloids* are determined by diluting 10 c.c. of the syrup with twice its measure of water, adding some citric acid and excess of ammonia, and agitating twice with ether-chloroform.[1] From the weight of the residue left on evaporating the solution, a deduction of 0·0057 gramme should be made for the *strychnine* present, the remainder being regarded as *quinine*. An actual separation can be made by precipitating the strychnine from a strongly acid solution by potassium ferrocyanide, as described on page 367.

Another method of separating the strychnine and quinine of

[1] From the aqueous liquid the total phosphoric acid may be thrown down by magnesia mixture.

Easton's syrup is to dissolve the ether-chloroform residue obtained as above in about 10 c.c. of water acidulated with a few drops of sulphuric acid. The solution is neutralised by ammonia and mixed with excess of ammonium oxalate. After standing twenty-four hours, the precipitated oxalate of quinine is filtered off, the mother-liquor removed by gentle pressure, and the precipitate washed once with a little cold water. It is then dried at 100° and weighed.[1] Its weight, multiplied by ·878, gives the quinine in the quantity of the sample operated on. The filtrate and wash-water are then treated with ammonia, shaken with ether-chloroform, and the dissolved alkaloid recovered as usual by evaporation of the solvent. The residue of alkaloid (consisting of strychnine, any amorphous alkaloid, and a mere trace of quinine) should be next twice treated with 3 c.c. of washed ether, which dissolves the amorphous alkaloid (and quinine), leaving the strychnine almost wholly undissolved.

For the determination of the small proportion of *strychnine* contained in Easton's syrup, Davies and Schmidt recommend the following colorimetric process devised by O. Eckenstein. The alkaloidal residue from 10 c.c. of syrup was dissolved in 31·25 c.c. of water acidulated with 1 c.c. of normal sulphuric acid, and 5 drops of the resultant solution were added to 4 c.c. of concentrated sulphuric acid tinted yellow with potassium bichromate. The colour produced after standing five minutes was then compared with the colour produced by known quantities of a very dilute solution of strychnine of known strength, in the same sulphuric acid coloured with bichromate. For quantitative purposes the method leaves much to be desired.

Easton's syrup is liable to give a deposit which sometimes contains quinine, and in other cases appears to be simply ferric phosphate. The tendency to deposit is often prevented by addition of a small quantity of hydrochloric acid.

Vermin-killers. An inquiry into the composition of various commercial vermin-killers containing strychnine was made by the author in 1889 (*Year-Book Pharm.*, 1889, page 434). The results showed them to consist of a mixture of strychnine with rice or wheat-starch, usually more or less coloured. Ultramarine was the most usual colouring agent, but prussian blue was met with in four preparations out of seventeen examined, in one case the powder containing both ultramarine and prussian blue. Carmine

[1] The mode of operating described in the text is due to B. W. Dwars. It would probably be better to wash the precipitate produced by ammonium oxalate, and then extract the quinine in the free state by agitating the precipitate with ammonia and ether.

was the colouring-matter of two preparations and soot of one.[1] In one instance, no colouring-matter whatever was present.[2]

Ultramarine is readily recognised in a vermin-killer by the peculiar shade of blue it communicates to the powder, and by the colour being wholly destroyed by agitation with dilute acid. If a little of the powder be placed on a silver coin and moistened with dilute acid, a brown stain will be produced on the coin by the sulphuretted hydrogen liberated from the ultramarine. Ultramarine retains its blue colour after ignition, whereas prussian blue leaves a brownish residue of oxide of iron, and indigo is more or less perfectly consumed, according to its purity. A decidedly ferruginous ash is left by some specimens of indigo. Prussian blue and indigo are unaffected by dilute hydrochloric acid. If the residue left after heating the powder with dilute hydrochloric acid be washed and treated with caustic soda solution, it will be unaffected if composed of indigo; but prussian blue will be turned brown, and the filtered liquid will contain a ferrocyanide, and hence will yield a blue or green precipitate or coloration when it is acidulated with hydrochloric acid and ferric chloride added.

The colour of a vermin-killer should not merely serve as a danger-signal, but be so chosen as to facilitate its detection in cases where it has been used for the purpose of suicide or murder. In a case in which the author was concerned, a murderer would probably have escaped conviction but for the detection of the blue colouring-matter in the stomach of his victim, which served to connect him with the administration of the poison.[3]

[1] This preparation consisted of strychnine, 5·8 per cent.; native barium carbonate, 45·0 per cent.; and wheat-flour and soot, 49·2 per cent. The object of the combination is not evident.

[2] Such a colourless preparation is highly dangerous. Teething powders are so generally coloured pink that they are not unfrequently asked for as "pink powders," and gray powders are equally common. The blue colouring-matters present considerable advantages over such pigments as soot and carmine, since no food, drink, or medicine has naturally a blue colour, and hence the tint at once attracts attention.

[3] Soot is unsuitable for colouring vermin-killers, as the identification of minute particles of carbon is difficult or impossible when mixed with food. Of the blue colouring-matters practically available, ultramarine is too readily destroyed by dilute acids and by the gastric juice, though it has the advantage of being readily detected, and of being undestroyed by ignition. Prussian blue is unaffected by acids, and not very readily affected by dilute alkaline liquids. Indigo resists alkalies still better, and is not affected by acids, except nitric acid, though it is at once bleached by oxidising agents, and is also decolorised by alkaline reducing agents. In minute quantity it is less easily recognised than prussian blue. A mixture of the three pigments would be

The toxicity of vermin-killers varies within wide limits. Of the samples examined by the author, the weight of strychnine contained in a packet of the powder varied from 0·60 to 4·18 grains, the retail price in each case being 3d. The proportion of strychnine ranged from 4·2 to 41·8 per cent.[1]

Strychnine can be determined in vermin-killers by exhausting a known weight of the dry powder with chloroform or benzene, and weighing the alkaloidal residue left on evaporating the solvent. The insoluble portion must be examined by the taste and oxidation-test, to ensure complete extraction and the absence of a salt of strychnine insoluble in the solvent used. An alternative, and in many respects preferable, method is to treat the vermin-killer with cold water acidulated with acetic acid, until the residual powder has no bitter taste, and gives no coloration by the oxidation-test. The solution is then treated with excess of ammonia, and the strychnine extracted by ether-chloroform, which is separated, evaporated to dryness, and the residue weighed.

Of vermin-killers containing strychnine, Battle's preparation is the best known, and most extensively used. The suicides

preferable to any one or two of them. "The most suitable pigment for colouring vermin-killers would be chrome-green (Cr_2O_3). In it we have a bright green pigment of high colouring power, quite insoluble in water and dilute acid and alkaline liquids. It is wholly permanent under all imaginable conditions, and is not affected by ignition. Chromium is not a natural constituent of the body, is not used internally as a medicine, and is not liable to be present accidentally, even in traces, in any beverage or article of food. It can be detected and determined with ease and certainty, even when present in very minute quantity. Owing to its insolubility, oxide of chromium would remain wholly unabsorbed if taken internally. Hence, if it were added to preparations of strychnine, &c., in a definite and invariable proportion, an estimate of the minimum amount of poison taken by a deceased person could be arrived at by determining the amount of chromium contained in the alimentary canal, even though the poison itself had been wholly absorbed or decomposed; and this could be effected with equal ease and certainty after prolonged inhumation, or even after cremation of the body."—A. H. Allen (*Year-Book Pharm.*, 1889, page 439).

[1] It does not follow that the vermin-killer which contains the greatest weight or the largest proportion of strychnine is the best for its purpose. Clearly, pure strychnine would be inefficient, and hence the object should be to compound a mixture which will have the most powerful poisoning effect compatible with its attractive and appetising character. To effect this, the bitter taste of the strychnine should be masked as far as possible, and a suitable odorant should be added. This object seems to have been recognised in one instance, for the powder contained sugar and had a powerful smell of assafœtida and oil of anise. Most of the vermin-killers examined by the author have been odourless.

due to it amount to many scores, and probably to hundreds. The colouring-matter of Battle's vermin-killer appears to have been uniformly prussian blue; but the following table shows that the composition ascribed to the preparation has varied in other respects at different periods :—

Authority.	A. Swaine Taylor.	A. J. Bernays.	T. Stevenson.	A. H. Allen.	Tardieu.	Woodman and Tidy.[1]
ate, . . .	1862.	1876.	1882.	1889.	...	...
rice of packet, .	3d.	3d.	6d.	6d.	...	...
eight of powder, .	13 grains.	15 grains.	25 grains.	21·5 grains.	20 grains.	...
olouring-matter, .	Prussian blue.	Prussian blue.	Prussian blue.	Prussian blue.	Prussian blue.	Prussian blue.
tarchy matter, .	Flour.	Wheat-flour.	...	Wheat-flour.	Potato-starch.	Flour.
trychnine ; grains,	0·75	1·6	2·5	2·4	1·5	...
trychnine ; per cent.,	5·8	10·7	10·0	11·2	7·7	23·0

The inert matter of vermin-killers usually consists of rice-starch, though in some cases wheat-flour, and occasionally oatmeal, is substituted. In one instance, the author found both rice and wheat starch, the powder being coloured with carmine.

Brucine. Brucia. $C_{23}H_{26}N_2O_4$; or $C_{22}H_{18}(OCH_3)_2$.

Brucine occurs in association with strychnine in *nux vomica*, St Ignatius' beans, and false angustura bark (page 360). The leaves of *strychnos nux vomica* are stated to contain brucine but no strychnine.

In chemical constitution, brucine appears to be a dimethoxy-strychnine.[2]

Brucia occurs as a bitter, white, odourless, crystalline or amorphous powder, or in groups of very delicate needles or four-sided prisms, containing 15·45 per cent. of water ($=C_{23}H_{26}N_2O_4+$

[1] Woodman and Tidy state that sugar is a constituent of Battle's vermin-killer. This was certainly not the case in 1889. The proportion of strychnine (23 per cent.) given by Woodman and Tidy is largely in excess of that found by other observers.

[2] Haussen finds that both strychnine and brucine yield by oxidation with chromic acid mixture a body containing $C_{16}H_{18}N_2O_4$, and hence that the difference between the two alkaloids must be sought in the residues, C_5H_4 and $C_7H_8O_2$ respectively, removed through the oxidation. The former of these is regarded as pointing to the presence of a benzene-nucleus in strychnine, which nucleus in brucine is dimethoxylated.

$4H_2O$).[1] When moderately heated the crystals melt and lose their water. According to Guy, brucine melts at 115°, and sublimes at 204° C., the sublimate being usually amorphous. According to Claus and Röhre, after drying at 150°, brucine melts at 178°.

Brucine is more soluble than strychnine in water, dissolving in 1050 parts of cold, and less than half that proportion of boiling water. In alcohol it dissolves very readily, a fact which is employed to separate it from strychnine. Brucine dissolves in 4 parts of chloroform, in 440 of ether, in 60 of benzene, and in 120 of petroleum spirit. It is insoluble in fixed caustic alkalies, and only sparingly in excess of ammonia.

Brucine is a weaker base than strychnine, but is not extracted from acidulated solutions by immiscible solvents. It resembles strychnine closely in its general characters, but is less poisonous, from 7 to 10 parts of brucine having the same physiological effect as 1 part of strychnine.[2] It is excreted far more rapidly than strychnine, so that when given by the stomach it produces little effect, though it is fatal when injected hypodermically (T. Lauder Brunton, *Jour. Chem. Soc.*, xlvii. 143).[3] Like strychnine, it is not acted on readily by cold sulphuric acid, or by caustic alkalies. It dissolves without decomposition in strong hydrochloric acid, and forms readily crystallisable and soluble salts.

On passing nitrogen trioxide into an alcoholic solution of brucine, brucine nitrate at first separates, but again dissolves, forming a red solution from which dinitrobrucine, $C_{23}H_{24}(NO_2)_2N_2O_4$, separates as a heavy, granular, blood-red precipitate. By washing with alcohol and ether, it is obtained as an amorphous, velvety, vermillion-coloured powder, easily soluble in water, sparingly in alcohol, and insoluble in ether. The chloroplatinate is obtained as a yellow precipitate on adding platinic chloride to the aqueous solution of dinitrobrucine (Claus and Röhre, *Ber.*, xiv. 765).

Analytical Characters of Brucine.

1. Brucine is precipitated in a free state on adding an alkali to the solution of one of its salts, and may then be taken up by

[1] From analyses of their platinous compounds, Koefoed is of opinion that commercial brucine contains two homologous alkaloids.

[2] According to Talk, the physiological activity of strychnine is 38½ times greater than that of brucine.

[3] T. J. Mays (*Jour. Physiol.*, viii. 391) finds that, when frogs are poisoned, brucine primarily affects the posterior and strychnine the anterior extremities; convulsions occur very early and invariably before death in strychnine poisoning, and very late or frequently not at all in brucine poisoning.

agitating the alkaline liquid with ether-chloroform in the same way as strychnine (see page 364).

2. Brucine forms a soluble chromate, a fact which is occasionally used to separate it from strychnine. A better separation is effected by crystallising the free alkaloids from hot alcohol, or by converting them into ferrocyanides (page 366).

3. When treated with concentrated sulphuric acid[1] and an oxidising agent, brucine does not give the coloured products so characteristic of strychnine.

4. The most satisfactory reaction of brucine is that with nitric acid. On adding a drop or two of cold nitric acid of 1·42 sp. gr. to an ether-chloroform residue, or other solid product containing brucine, a scarlet or blood-red coloration is produced, which on heating changes to yellowish red, and finally to yellow.[2] If the mixture be now cooled and treated very cautiously with stannous chloride (or other reducing agent, such as sodium thiosulphate), a purple coloration is produced, which is destroyed by excess of either nitric acid or the tin salt.[3]

The red coloration of brucine by nitric acid may likewise be developed by dissolving the alkaloid in strong sulphuric acid in a test-tube, and allowing nitric acid to run on to the surface of the heavier liquid. A red zone, passing to yellow, will be produced at the junction of the two liquids. If cold nitric acid be added to solid brucine, so as to develop the red colour, and the moisture be then largely diluted with water, a body called kakotelin, $C_{20}H_{22}(NO_2)_2N_2O_5$, separates in yellow flocks. The filtered liquid, after neutralisation by ammonia, gives a precipitate of calcium oxalate on being treated with calcium chloride. The precipitated kakotelin may be dissolved in dilute hydrochloric acid, and crystallised therefrom in orange-red or yellow scales.

The production of a red colour with nitric acid, accompanied by a formation of oxalic acid and yellow scales or crystals, insoluble in water but soluble in dilute acids, constitutes a combined reaction which is peculiar to brucine.

5. Brucine dissolves in chlorine-water with red colour. On evaporation, dichlorobrucine, $C_{23}H_{24}Cl_2N_2O_4$, remains as a reddish brown, amorphous mass.

6. Potassium bichromate throws down from solutions of brucine

[1] According to some observers, strong sulphuric acid imparts to brucine a rose colour, which changes first to yellow and then to yellowish green.

[2] Strychnine, on the contrary, gives no coloration with cold nitric acid, but developes a yellow colour on warming.

[3] The orange colour produced by adding nitric acid to morphia remains unchanged on addition of stannous chloride.

salts, even when very dilute, a yellow precipitate of brucine chromate, insoluble in acetic acid, but soluble with deep red colour in strong nitric acid. The microscopic appearance of brucine chromate is characteristic, and, together with its behaviour with nitric acid, distinguishes the precipitate from all others produced by the reagent.

7. The microscopic appearances of the precipitates produced in brucine solutions by platinic chloride and potassium ferricyanide are also highly peculiar.

8. Potassium ferrocyanide only slowly precipitates acidulated brucine solutions, and affords the best means of quantitatively separating brucine from strychnine *(page 366).*

Nux Vomica.[1] Poison-nuts. Quaker Buttons.

The seeds of *Strychnos nux vomica* are known by the above names. Their appearance is highly characteristic. They have no odour, but taste intensely bitter.[2]

If powdered nux vomica seeds be moistened with water and examined with a low power, the characteristic fibrous hairs can be readily recognised. They acquire a yellow colour on adding iodised potassium iodide, while the rest of the powder becomes brown. Touched with strong nitric acid, the powder acquires an orange-red colour, gradually destroyed on adding stannous chloride.

Nux vomica contains, in addition to the usual plant-constituents, the poisonous alkaloids strychnine and brucine,[3] a glucoside called loganin, and a peculiar acid named strychnic or igasuric acid.

STRYCHNIC or IGASURIC ACID appears to be a variety of tannin. It was obtained by Höhn (1873) as an amorphous yellowish-white mass of strongly acid and somewhat astringent taste. It gives a dark green coloration with ferric chloride, a white precipitate with lead acetate, and rapidly reduces ammonio-nitrate of silver.

[1] French; *Noix vomiques.* German; *Krähenaugen, Brechnuss.*

[2] The powder of nux vomica has a grayish-buff colour, and, in the experience of the author, has been sold by a registered druggist in mistake for jalap. Death has been caused by the sale of nux vomica for liquorice powder, which, by artificial light, is of somewhat similar appearance (*Pharm. Jour.*, [3], xvi. 401).

[3] If a microscopic section of nux vomica be treated with petroleum spirit to remove the fat, the parts containing brucine will then assume a bright red colour on being moistened with a mixture of selenic and nitric acids. To detect strychnine, the section is treated in succession with petroleum spirit and absolute alcohol (to remove sugar and brucine), and then tested with a solution of cerium sulphate in sulphuric acid (O. Lindt, *Chem. Centr.*, 1884, page 498).

Loganin exists in nux vomica seeds, but more largely (4 to 5 per cent.) in the pulp in which they lie embedded in the fruit. Dunstan and Short (*Pharm. Jour.*, [3], xiv. 1025) obtained loganin in prismatic crystals by cooling the liquid obtained by exhausting this substance with chloroform-alcohol (4 : 1). After recrystallisation from alcohol, the crystals contained $C_{25}H_{34}O_{14}$, an empirical formula identical with that of arbutin, from which, however, loganin is distinguished by its much higher melting-point (above 200° C.), and by not yielding quinol with dilute sulphuric acid.

Loganin is readily soluble in water and alcohol, but less so in ether, chloroform and benzene. It developes no colour with nitric acid or other oxidising agents, and the aqueous solution is not affected by solutions of lead, iron or silver, and does not reduce Fehling's solution. When gently warmed with strong sulphuric acid, loganin gives a fine red colour, changing to purple on standing. When boiled with dilute sulphuric acid, it yields a reducing glucose and loganetin, which latter body behaves with solvents and reagents very similarly to loganin itself.

For the *assay* of nux vomica, Dunstan and Short (*Pharm. Jour.*, [3], xiii. 665, 1055) recommend that 5 grammes of the finely-divided seeds (previously dried at 100° C.) should be exhausted in a Soxhlet tube or its equivalent, for one or two hours, with a mixture of 40 c.c. of chloroform and 10 of alcohol.[1] The solution is agitated with 25 c.c. of dilute sulphuric acid (5 per cent.), and the chloroform separated and again agitated with 10 c.c. of dilute acid. The separated acid solutions are filtered, if necessary, rendered alkaline with ammonia, and shaken twice with chloroform, using 15 c.c. each time. The chloroformic solution is separated, filtered, evaporated, and the residue dried at 100° for about an hour, or till constant in weight. The following results were obtained :—

Description of Sample.	Date of Collection.	Total Percentage of Alkaloids.
Bombay, fine, ...	1877	3·46
Bombay, ordinary, . . .	1877	3·14
Bombay, ...	1883	3·90
Cochin, ...	1887	3·04
Cochin, ...	1883	3·60
Madras, ...	1877	2·74
Madras, ...	1883	3·15
Average, ...		3·29

[1] This mixture is described by the authors as one containing 25 per cent. of alcohol.

The alkaloid in powdered commercial nux vomica ranged from 2·56 to 3·57 per cent.[1]

Ether-chloroform may be advantageously substituted for unmixed chloroform in the foregoing process, and the alkaloids may be conveniently titrated with a standard mineral acid and methyl-orange instead of being weighed. One c.c. of decinormal acid neutralises 0·0364 gramme of a mixture of brucine and strychnine in molecular proportions (334 : 394). When desired, the strychnine and brucine may be separately determined as described on page 367.

Extract of Nux Vomica, B.P., is directed to be prepared by exhausting the dried and powdered seeds with somewhat diluted spirit (4 : 1), and evaporating the filtered liquid. Formerly the extract varied considerably in strength, twelve specimens of the commercial article examined by Dunstan and Short in 1884 (*Pharm. Jour.*, [3], xiv. 443) containing proportions of total alkaloids ranging from 10·32 to 17·54 per cent.; while the ratio of strychnine to brucine varied from 1 : 1 up to 1 : 1·79.[2] On the other hand, the proportion of water only varied between 13·6 and 19·7 per cent.[3]

In the *Pharmacopœia* of 1885, the extract is directed to be standardised so as to contain 15 per cent. of total alkaloids. For its assay, 10 grains of the extract are directed to be dissolved in ½ oz. of water, heating gently if necessary, and a solution of 30 grains of sodium carbonate in ½ oz. of water added. The solution is then agitated with ½ oz. of chloroform, which extracts the alkaloids. This treatment should be repeated (*Pharm. Jour.*, [3], xix. 625), after which the chloroform is shaken with dilute acid, and this solution extracted with chloroform and ammonia in the manner already described (page 385).

As strychnine is greatly more active than brucine, and the relative proportions of the two alkaloids in the extract are by no means constant, it is questionable whether it would not be pre-

[1] Powdered nux vomica has frequently been dried at a temperature above 100°, in which case the chloroform-alcohol extract often contains colouring-matter which ultimately contaminates the alkaloid. In such cases the brown colour may be removed by agitating the chloroform-alcohol solution with an aqueous solution of crystallised sodium carbonate (5 per cent.) before treating it with dilute acid.

[2] Beckurts (*Pharm. Jour.*, [3], xx. 341) found in five samples of nux vomica extract the ratio of strychnine to brucine varied only between 43 : 57 and 54 : 46.

[3] The absence of relation between the total extractive matter and the alkaloids of nux vomica renders the official method of standardising the extract very unsatisfactory.

ferable to ascertain the proportion of actual strychnine rather than that of the total alkaloids.

G. F. Schacht (*Pharm. Jour.*, [3], xiv. 851) recommends for the rapid assay of nux vomica extract that 1 gramme be dissolved in 30 c.c. of water, the solution acidulated with 1 c.c. of hydrochloric acid, warmed gently for half an hour, and allowed to cool. It is then filtered and made up to 100 c.c. Ten c.c. of this solution is then titrated with $\frac{N}{100}$ Mayer's solution (page 139), each c.c. of which represents 0·00184 gramme of mixed strychnine and brucine.[1] The results by this process are stated to agree closely with those obtained by the gravimetric method.

Nux vomica extract contains from 9 to about 20 per cent. of water, and some specimens lose and others gain weight on exposure.

Tincture of Nux Vomica, B.P., is directed to be prepared by dissolving the extract in slightly diluted spirit, so as to contain 1 grain of total alkaloids in each fluid ounce; equivalent to 0·229 grain per 100 measures. Dunstan and Short (*Year-Book Pharm.*, 1883, p. 476) found the specific gravity of twelve commercial tinctures, obtained from the principal London manufacturers, to vary from ·8377 to ·8552; the proportion of strychnine from 0·046 to 0·131, with an average of 0·080 per cent.; the brucine from 0·075 to 0·239, averaging 0·130 per cent.; and the total alkaloid from 0·124 to 0·360, with an average of 0·218 per cent. Before 1885, when the tincture was directed to be prepared from a duly standardised extract, its strength was very variable.[2] The tincture of nux vomica may be assayed by evaporating the spirit from 50 c.c., treating the residue with dilute sulphuric acid and chloroform, separating the acid, and extracting the alkaloids by ammonia and chloroform.

Alkaloids of Curare.

The Indian arrow-poison[3] known as curare, curari, wourali, woorara, or urari is a poisonous extract prepared

[1] The solution is prepared with 1·355 gramme of mercuric chloride and 4·98 of potassium iodide in the litre.

[2] The preparation of the tincture of nux vomica from a standardised extract has apparently failed to secure uniformity in its composition; for of twenty-four samples of the commercial tincture purchased by N. H. Martin in 1886, nine months after the publication of the new edition of the *Pharmacopœia*, eleven showed by their pale yellow colour that they had been prepared by the old process from the seeds, and contained from 0·119 to 0·288 per cent. of total alkaloids; while the percentage of total alkaloids in the thirteen samples which by their light brown colour showed they had been prepared from the extract, ranged from 0·196 to 0·313 per cent. (*Year-Book Pharm.*, 1886, page 507).

The intensely active arrow-poison used by the pigmies met with by

from the bark of *Strychnos toxifera*, a native of Guiana, together with other vegetable extracts.[1] It occurs in commerce as a black, shining, brittle, resinoid mass, of an intensely bitter taste. About 83 per cent. is soluble in water, and 79 in diluted spirit. A mixture of glycerin and diluted spirit dissolves 85 per cent., but it is only slightly acted on by ether or chloroform, even in presence of a free alkali. Curare, as imported, varies much in strength, and often contains calcium carbonate and phosphate. It is exceedingly poisonous, and should be handled with the utmost care. Curare should never be allowed to come in contact with a cut or scratch, and, indeed, should never be touched with the naked fingers, or powdered or manipulated in the dry state.

"Much doubt exists as to the true nature of woorara. According to Waterton it is prepared from several different plants, two species of poisonous ants, and the fangs of certain snakes; while Schomburgk states that it consists of vegetable matter alone, and chiefly of the bark of *Strychnos toxifera*. . . . That there are at least several varieties of this substance current among the different tribes of Indians seems to be fully established . . .; and it is even probable that each tribe has its own method of preparing the poison" (T. G. Wormley, *Micro-Chemistry of Poisons*).

Curarine exercises both a paralysing and tetanising action, but it appears to owe its chief poisonous properties to its action on the nerves of motion, which it paralyses, so that an animal under its influence dies of suffocation from paralysis of the muscles of the chest. Hence its physiological effects closely resemble those produced by methyl-strychnine. According to J. Tillie, when the difficulties besetting the examination of the action of curare on the spinal cord are avoided, curare produces tetanus just like strychnine. Curare appears not to act as a poison when taken into the stomach, but when employed as a hypodermic injection ·015 grain has been found fatal to a rabbit, and ·004 grain to a frog. If, after administration of curare, life be maintained by artificial respiration, symptoms of *diabetes mellitus* are observed, and the urine is found to contain sugar.

Neither strychnine nor brucine has been detected in curare, and that the paralysing effects of the preparation are not due to methyl-strychnine is apparently proved by the superior toxicity of the vegetable extract. J. Tillie (*Jour. Anat. and Physiol.*, 1890) attributes both the paralysing and tetanising action of curare to

H. M. Stanley in Central Africa is compounded from five plants. Its toxic action is believed by E. M. Holmes to be due to erythrophlœine and strychnine (*Pharm. Jour.*, [3], xxi. 917).

[1] See a valuable paper by J. Moss, *Pharm. Jour.*, [3], viii. 121.

curarine, but it seems not improbable that the preparation contains at least two active alkaloids, one having a paralysing and the other a tetanising action (as is the case with Calabar bean).[1]

Curare has been proposed as a remedy for hydrophobia and as an antidote to poisoning by strychnine.

CURARINE is the name given to the physiologically active base of curare, and the improbable formula $C_{18}H_{35}N$ has been ascribed to it. Curarine has been variously described by different observers, and it appears certain that the products have been of very discordant characters. Curarine is described (1865) by Preyer (*Chem. News*, xii. 10) as crystallising in very hygroscopic four-sided prisms, having a bitter taste, freely soluble in water and alcohol, only slightly so in chloroform and amylic alcohol, and insoluble in ether, benzene, turpentine and carbon disulphide.

The aqueous and alcoholic solutions of curarine have a bitter taste and faintly alkaline reaction. The base is said to form crystallisable salts with hydrochloric, nitric, and acetic acids.[2] The commercial curarine prepared by Merck, according to Böhm's method, is described as a yellowish brown, amorphous powder of intensely bitter taste, easily soluble in water and alcohol, but insoluble in ether. It shows no perceptible alkaline reaction, and forms no true salts; but on evaporating an aqueous solution in dilute acid to a syrup, acicular crystals of an inactive decomposition-product are formed, whereas the lethal dose for guinea-pigs of curarine itself is stated at 0·00035 gramme per kilogramme of weight. Concentrated sulphuric acid dissolves Merck's curarine with crimson colour, changed to bluish by potassium bichromate.

With strong nitric acid Preyer found curarine to give a purple coloration, and with concentrated sulphuric acid a magnificent and lasting blue colour. C. Bernard found the colour with sulphuric acid to be a carmine-red.

If a filtered and highly concentrated solution of curarine be mixed with dilute glycerin, and a saturated solution of potassium bichromate added, amorphous curarine chromate is precipitated. Even after solution in boiling water it is again deposited in an amorphous state, a fact which distinguishes it from strychnine

[1] That the tetanising action of curare is due to the species of *Strychnos* employed for its preparation, and not to picrotoxin or other principles derived from the various plants sometimes used in conjunction with it, is proved by the fact that a genuine specimen of the bark of *Strychnos toxifera* produced the same symptoms (J. Tillie, *Jour. Anat. and Physiol.*, xxv. 42; see also Nikolski and Dogiel, *Year-Book Pharm.*, 1891, page 198).

[2] According to Sachs (*Annalen*, cxci. 254), Preyer's crystalline curarine sulphate consisted of impure calcium phosphate (?) with mechanically adhering curarine.

chromate, which forms well-defined crystals. Curarine chromate is more soluble in water than is strychnine chromate, and is never perfectly precipitated even by addition of glycerin or alcohol.

If the precipitate of curarine chromate be kept for some time it decomposes, but if treated without delay with concentrated sulphuric acid it developes a magnificent blue colour, which is often violet in the presence of impurities. (Pelican observed a brilliant red coloration.) The reaction simulates that obtained in a similar manner with strychnine, but curarine can be separated from strychnine by rendering the cold solution alkaline with ammonia, and then filtering. Strychnine will be found in the precipitate, whilst the curarine will remain in the liquid, owing to its solubility in water. The filtrate may be agitated with chloroform or benzene to remove any trace of strychnine, the aqueous liquid concentrated and the curarine converted into chromate and tested further, as already described.

Curarine is very unstable, and hence its solution should be subjected to as little manipulation as possible.

CURINE exists, according to Böhm (*Ber.*, xx. 143), together with curarine in many specimens of commercial curare. Curine is said to exist in the aqueous extract of curare, though in some cases dilute sulphuric acid is requisite for its complete solution. Upon rendering the liquid slightly alkaline with ammonia, a dirty green precipitate of impure curine is found, which, by successive purifications with ether, alcohol, and again with ether, may be obtained in a micro-crystalline condition. Curine is described as melting at 160° to a clear liquid, and being slightly soluble in cold water, freely in alcohol, chloroform, and dilute acids, but less readily in ether. The most characteristic reaction of curine is the formation of a voluminous white precipitate with metaphosphoric acid. Curine itself is stated by Böhm to be physiologically inactive (in doses of 5 to 10 milligrammes), but by treating it with methyl iodide he obtained the hydriodide of a new base which possessed an intense curare action, 1 milligramme killing a guinea-pig (weighing 1600 grammes) in one hour. J. Tillie (*Journ. Anat. and Physiol.*, xxv. 42) states that curine has no apparent action on motor nerves, but when hypodermically injected acts on the hearts of both frogs and rabbits as a paralysant similar to veratrine or digitalis. As curine is liable to be present in curare in very variable proportions, its possible presence in commercial curarine must not be overlooked.

CINCHONA ALKALOIDS.[1]

The various species of the family of plants known as the *Cinchonaceæ* yield an extraordinary number of closely analogous alkaloids. These bases exist chiefly, though not wholly, in the bark of the trees, and are remarkable for their valuable febrifuge properties.

The constitution of the cinchona bases is at present very imperfectly understood. Quinamine and cupreine are known to contain hydroxyl-groups, and quinine and cinchonine and their isomers have been proved to be derivatives of quinoline. An abstract of the existing knowledge of the subject is given on page 168.

Any satisfactory classification of the cinchona bases in the present imperfect state of our knowledge of their constitution, and in some cases even of their empirical formulæ, is manifestly impossible. Isomerism is common, and on slight provocation quinine and some others suffer polymerisation, with or without losing the elements of water, forming amorphous "apo-" or anhydro-bases.

Perhaps the most suggestive method of classifying the cinchona bases and their allies is to arrange them according to the number of atoms of oxygen in the molecule, and subdivide these classes according to other analogies.

The following (pages 392, 393) is a tabular list of the alkaloids hitherto isolated from the various species of cinchona and allied barks. It contains the names of all the natural cinchona bases, the existence of which as chemical individuals has been fairly well established up to the present time; but it must not be supposed to include all that actually exist.

As is evident from the table, isomerism is very common among the cinchona bases. Thus the two best-known bases are qui*nine* and cincho*nine*. Isomerides of these bases coexist with them in the bark, and are called respectively qui*nidine* and cincho*nidine*. It is probable, however, that the base usually termed cinchonidine presents the closest parallelism with quinine, and that cinchonine is the analogue of quinidine.

The four bases above mentioned are the chief crystallisable alkaloids of cinchona barks, but there exist with them, or are formed in the process of manufacture, certain amorphous isomerides called respectively qui*nicine* and cincho*nicine*. It is doubtful how far these bases pre-exist in the bark, the natural amorphous alkaloids being probably the anhydro-derivatives *diquinicine* and

[1] The author is indebted to Dr B. H. Paul and Mr A. J. Cownley for the perusal and correction of this section.

TABLE OF CINCHONA BASES.

Alkaloid.	Formula.	Chief Source.	Melting Point, °C.	Optical Rotation, S_D.1	Other Characters.
I. CINCHONINE CLASS—					
Paricine,	$C_{16}H_{18}N_2O$	*C. lutea* and *C. succirubra* from Darjeeling.	130	0	Pale yellow, amorphous, bitter powder. Sparingly soluble nitrate.
Cinchotine,		Crude cinchonine sulphate.	277	+	Slender prisms and scales.
Cinchopamine,		*Remijia Purdieana.*	194	+121·1	Very poisonous. Hexagonal prisms. No thalleioquin reaction. Page 438.
Hydrocinchonine,	$C_{19}H_{24}N_2O$	*C. cuprea.*	256	..	Yellow, amorphous powder.
Hydrocinchonidine, or Cinchamidine,		Mother-liquors of homocinchonidine.	229	−98·4	Plates or flat needles. Not fluorescent.
Cinchonine,	$C_{19}H_{22}N_2O$	Various species of *Cinchona.* Almost always present.	255	+226·5	Rhombic prisms. Page 431.
Cinchonidine,		Especially *C. rubra.*	202	−70	Prisms. Page 428.
Homocinchonidine,	.. ..	With cinchonidine.	207	−107	Prism or plates. Not fluorescent. No thalleioquin reaction.
Cinchonicine,	.. ..	By heating cinchonine.	50	+20·1	Amorphous. Crystallisable salts. P. 435.
Paytine,	$C_{21}H_{24}N_2O$	From white bark of Payta.	156	−49·5	Crystallises with 1 aqua in fine prisms.
Paytamine,			..	..	Amorphous. Amorphous salts.
II. QUINAMINE CLASS—					
Quinamine,	$C_{19}H_{24}N_2O_2$	*C. succirubra* from Brit. India and Java.	172	+104·5	Long prisms. Page 427.
Conquinamine,		*C. officinalis, C. calisaya.*	121	+204·6	Long shining, triclinic prisms. Page 427.
Javanine,	.. ..	*C. calisaya* from Java.	..	..	*a.* Rhombic plates. Solution in H_2SO_4 intensely yellow.
Cupreine,	$C_{19}H_{22}N_2O_2$	*C. cuprea* or *Remijia pedunculata.*	198	−175·3	*a.* Grouped prisms. Page 438.

TABLE OF CINCHONA BASES—*continued.*

Alkaloid.	Formula.	Chief Source.	Melting Point, °C.	Optical Rotation, S_D.[1]	Other Characters.
III. QUININE CLASS—					
Hydroquinine,	$C_{20}H_{26}N_2O_2$	In mother-liquors from quinine *sulphate.*	168	-142·2	Bitter needles. Fluorescent. Thalleioquin reaction. Page 424.
Hydroquinidine,			166	+	Needles or tables. Fluorescent. Thalleioquin reaction.
Quinine,	$C_{20}H_{24}N_2O_2$	*Calisaya officinalis, &c.*	172	-145·2	Page 397.
Quinidine,			168	+236·8	Page 425.
Quinicine,		By heating quinine sulphate.	60	+44	Amorphous or oil. Non-fluorescent. P. 434.
IV. CUSCONINE CLASS—					
Chairamine,	$C_{22}H_{26}N_2O_4$	*Remijia Purdieana* (Cusco or False Cuprea Bark).	233	+100	*a.* Needles or prisms containing 1 aqua.
Conchairamine,			120	+68·4	*a.* Prisms.
Chairamidine,			127	+7·3	*a.* Amorphous powder.
Conchairamidine,			114	-60	*a.* Crystallisable.
Concusconine,			144	+40·8	*a.* Monoclinic prisms.
Aricine	$C_{23}H_{26}N_2O_4$		188	-58·2	*a.* Non-bitter, shining prisms. Acetate crystalline, nearly insol. in cold water.
Cusconine,	$C_{23}H_{26}N_2O_4$		110	-54·3	*Monoclinic* plates with 2 aqua. Not fluorescent.
Cusconidine,			..	..	Yellow, amorphous.
Cuscamine,	.. ..	*C. Pelletierana.*	218	..	Flat prisms.
Cuscamidine,			..	..	.. ..
V. ANHYDRO-BASES—					
Dicinchonicine,	$C_{38}H_{44}N_4O_2$	*C. rosulenta* and *C. succirubra.*	40	+66	Yellowish, amorphous. No thalleioquin *reaction.* Page 435.
Diquinicine,	$C_{40}H_{46}N_4O_3$	*C. rosulenta* and "quinoidine."	..	+	Amorphous, and amorphous salts Fluorescent. Thalleioquin reaction.

[1] The values for specific rotatory power refer to solutions of the free alkaloids in nearly absolute alcohol.

dicinchonicine, and distinct from the amorphous products formed from the crystallisable bases by the action of heat or acids.

In addition to these isomers and anhydro-derivatives of the cinchona bases, there exist various homologues and isologues of them. Quinine itself is probably a methyl-cupreine and a methoxy-cinchonine.

Certain of the cinchona bases (*e.g.*, cupreine) exhibit a remarkable tendency to form stable crystalline compounds with other of the bases. It is probable that the existence of these remarkable compounds, having different physical properties in the form of salts as well as in the free state, has led to the isolation and description of various bases which will hereafter be found to be compounds.

The less important cinchona bases have no recognised position in commerce or medicine, but they are liable to be present to a greater or less extent in specimens of commercial alkaloids called by the better-known names. Commercial quinine is liable to retain traces of cinchonine, quinidine and hydroquinine, and generally contains notable proportions of cinchonidine. Hydrocinchonidine is sometimes present in commercial cinchonidine, while quinidine contains hydroquinidine and hydroquinine. Quinamine and conquinamine are probably not unfrequently present in commercial cinchona alkaloids.

General Properties of Cinchona Bases.

The cinchona alkaloids all have well-defined basic characters, some of them being sufficiently powerful to displace ammonia from its compounds. Their salts are usually crystallisable.

In the free state, the cinchona alkaloids are colourless or faintly-yellow solids, often readily fusible, but not volatile without decomposition. They have generally but little solubility in water, but dissolve more readily in alcohol, and generally with great facility in ether and chloroform. Such as are soluble in the last two liquids are removed from their ammoniacal solutions by agitation with ether or chloroform, but in no case will ether or chloroform remove them from an aqueous *solution* acidulated with sulphuric or hydrochloric acid. On the other hand, the anhydrous sulphates of many of the cinchona alkaloids are soluble in chloroform, and still more readily in a mixture of chloroform and absolute alcohol. This fact is sometimes utilised for detecting adulterations (p. 417).

The solutions of some of the cinchona alkaloids in excess of dilute sulphuric acid exhibit a strong blue fluorescence, which is visible even in very dilute liquids. This fluorescence is destroyed by adding an excess of chloride of sodium or other haloid salt.

The solutions of the cinchona alkaloids exert a well-marked rotatory action on polarised light, the rotation being in some cases right- and in others left-handed. The specific rotation is affected in a remarkable manner by the solvent employed and by the proportion of free acid present, which circumstances greatly reduce the practical value of the optical activity for the identification and quantitative determination of the unmixed alkaloids.

On adding a fixed alkali, alkaline carbonate or ammonia to the solution of a salt of one of the cinchona bases, the sparingly soluble alkaloid is usually separated in a free state, and is in some cases soluble in an excess of the precipitant. On agitating the alkaline liquid with chloroform, the precipitated alkaloid is usually dissolved,[1] and may be recovered in a free state by separating the chloroform, and evaporating it to dryness at a steam-heat. By adding more chloroform to the aqueous liquid, and repeating the agitation, the complete extraction of the alkaloid may be ensured, and the process made quantitative (see page 419). Ether may be substituted for chloroform in the case of quinine and other alkaloids readily dissolved by it.

The cinchona bases are tertiary amines; for when treated with an alkyl iodide they form additive-compounds which are converted by treatment with oxide of silver into powerful soluble bases analogous to the tetrethyl-ammonium hydroxide (page 19).

Many of the cinchona alkaloids form two series of salts; neutral (improperly called "basic"), and acid salts. The neutral sulphates of the cinchona alkaloids have, when anhydrous, the general formula $B_2H_2SO_4$. They have a neutral reaction to litmus and methyl-orange, and are generally very sparingly soluble in water; but the corresponding acid or bi-sulphates (BH_2SO_4) are generally readily soluble. In some cases still more acid sulphates are known.

The sulphates of many of the cinchona bases possess the property of combining with iodine, the compounds produced being in some cases of a very complex character. Certain of these "iodo-sulphates," of which the quinine compound or herepathite is the type, possess the remarkable optical properties of the tourmaline (see page 403).

When a salt of one of the natural cinchona bases is heated for a prolonged period to a high temperature, the alkaloid undergoes a curious change. It becomes incapable of crystallising, a property sometimes extending to its salts. The change occurs most readily by exposing the acid sulphate of the alkaloid to a temperature of 100° till anhydrous, and then increasing the heat for some time

[1] This is not the case with cupreine and some other alkaloids, which form definite compounds with the fixed alkalies in the same manner as morphine.

to about 130° C. No means are at present known by which the modified alkaloid can be restored to its original crystallisable condition.

When the cinchona bases are heated with strong hydrochloric acid (sp. gr. 1·125) to 150° for six to ten hours, they are converted into apo- or anhydro-derivatives of basic character, the change in the case of quinine and quinidine being attended with evolution of methyl chloride (Hesse, *Annal.*, ccv. 314).

When the sulphates of quinine, cinchonine, and cinchonidine are dissolved in concentrated sulphuric acid at the ordinary temperature, they are converted into "iso-bases" (Hesse, *Annal.*, ccxliii. 131), which differ in several respects from the parent alkaloids. Hydroquinine, hydroquinidine, and hydrocinchonidine are converted by the same treatment into the corresponding sulphonic acids, which are compounds of distinct basic character.

With platinic chloride, the hydrochlorides of the cinchona bases form chloroplatinates of the general formula BH_2PtCl_6, but many of them also form salts containing $B_2H_2PtCl_6$. Salts of this constitution are produced on adding sodio-platinic chloride to neutral solutions of quinine, quinidine, cinchonidine, and homocinchonidine (Hesse, *Annal.*, ccvii. 922). The auro-chlorides of the cinchona bases are mostly unstable, and liable to speedy decomposition with separation of finely-divided metallic gold.

Certain of the cinchona bases give a deep green coloration or precipitate when their solutions are treated with chlorine or bromine water, and ammonia subsequently added. This reaction is known as the "thalleioquin test" (see also page 401).

Most of the cinchona bases are very completely precipitated by tannic and picric acids, potassio-mercuric iodide, and certain other reagents. These reactions are sometimes used for their detection and separation.

On treatment in solution with bromine-water in slight excess, the cinchona bases are converted into bromo-derivatives. The number of atoms of bromine taken up varies with the constitution of the alkaloid. According to T. Fawssett (*Pharm. Jour.*, [3], xix. 915), quinine, quinidine, and cupreine react with approximately Br_6, hydroquinine with Br_4, and cinchonine, cinchonidine, and "amorphous quinine" with Br_2. On heating the cinchona bases, or their hydrochlorides or sulphates, with acetic anhydride to about 80° C. for a few hours, they are converted into acetyl-derivatives (Wright and Beckett, *Jour. Chem. Soc.*, xxix. 655; O. Hesse, *Annal.*, ccv. 314). With the exception of the acetyl-derivative of quinine, all these compounds are amorphous. They can be dried at 100° without change, are readily soluble in

dilute acids, and are thrown down as resinous precipitates by alkalies. On treatment with alcoholic potash they are hydrolysed into acetic acid and the original bases. The acetyl-derivatives of quinine and quinidine give the thalleioquin reaction.

The more important properties of the leading cinchona alkaloids may be summarised as follows :—

A
- *Hydrated crystals* are formed by Quinine, Quinidine, Paytine, Cupreine, Cusconine, Chairamine.
- *Anhydrous crystals* are formed by Cinchonine, Cinchonidine, Quinamine.
- *No crystals* are formed by Paricine, Quinicine, Diquinicine, Dicinchonicine.

B
- *Readily soluble in Ether* :—Quinine, Quinamine, Paytine, Quinicine, Javanine.
- *Sparingly soluble in Ether* :—Cinchonidine, Quinidine, Cupreine.
- *Almost insoluble in Ether* :—Cinchonine.

C
- *Dextro-rotatory* solutions in alcohol are formed by Cinchonine, Cinchonamine, Quinamine, Quinidine, Chairamine, Quinicine, Diquinicine.
- *Lævo-rotatory* solutions in alcohol are formed by Cinchonidine, Hydrocinchonidine, Homocinchonidine, Paytine, Cupreine, Quinine, Hydroquinine, Cusconine, Aricine.

D
- *Fluorescent* solutions in dilute sulphuric acid are formed by Quinine, Quinidine, Hydroquinine, Hydroquinidine, Diquinicine.
- *No fluorescence* is exhibited by solutions of Cinchonine, Cinchonidine, Hydrocinchonidine, Homocinchonidine, Quinamine, Quinicine, Dicinchonicine, Cusconine, Cupreine.

E
- *Thalleioquin* is formed by Quinine, Quinidine, Quinicine, Diquinicine, Hydroquinine, Hydroquinidine, Cupreine.
- *Thalleioquin* is *not* formed by Apoquinidine, Cinchonine, Cinchonidine, Homocinchonidine, Hydrocinchonidine, Cinchonicine, Dicinchonicine, Quinamine, Cinchonamine.

Quinine. Quinia.

$C_{20}H_{24}N_2O_2$; or $C_9H_6(O.CH_3)N.C_9H_{11}(OH)N.CH_3$.

Quinine is the most important of the cinchona bases, and appears to possess the most powerfully febrifuge properties. Its mode of preparation from the bark is based on the same principles as its determination in the same.[1]

[1] The finely-powdered bark is ground to a thin paste with lime, caustic soda, or sodium carbonate, and extracted with warm paraffin oil. On standing the oil separates, when it is run off and shaken with sulphuric acid ; this solution is boiled, and whilst boiling is neutralised with sodium carbonate and allowed to cool. Quinine sulphate crystallises out on cooling, whilst cinchonidine, cinchonine, and quinidine remain in solution as sulphates. The quinine sulphate is purified by recrystallisation after treatment with animal charcoal. The mother-liquor containing the other alkaloids is treated with caustic soda,

The chemical constitution of quinine is not thoroughly understood, but such knowledge as exists is epitomised on page 168. The complete synthesis of the alkaloid has not hitherto been effected, but cupreine has been apparently converted into quinine by the introduction of a methyl-group.[1] Two distinct bodies isomeric with quinine have been synthetically prepared (page 169).

Free quinine usually appears as an amorphous or resinous mass. In commerce the free alkaloid is usually met with as a coarse powder, having a brownish yellow tint owing to a trace of colouring-matter. It may also be obtained as a fine white powder.

From alcohol and some other solvents quinine may be obtained in crystals, but on the evaporation of its ethereal solution it separates as a gelatinous or resinoid mass, which is never crystalline. This behaviour is important, as most other cinchona bases give crystalline ether-residues.

As obtained by the precipitation of one of its salts by an alkali, quinine forms a bulky, white precipitate, which coagulates into a resinoid mass by very slight elevation in temperature. According to O. Hesse the precipitate at first formed at the ordinary temperature is amorphous and anhydrous, but it soon takes up water and becomes crystalline. It then contains 3 aqua. If the ammonia be added in large excess, and the solution is not too concentrated, the trihydrate is obtained in small needles,

and extracted with weak alcohol. Of the three bases precipitated by the alkali, quinidine and cinchonidine are dissolved by the spirit, whilst cinchonine is left behind; the two former can then be separated by means of their neutral tartrates, that of quinidine being considerably the more soluble.

Chemically pure quinine is manufactured by preparing the acid sulphate, which after undergoing sufficient purification is reconverted into the neutral salt. The consumption of quinine amounts to 200,000 kilos. annually. The Ceylon bark yields about 2·4 per cent. of quinine sulphate; Java bark, 4 to 9 per cent., and even up to 13 per cent. The more recent cultivations of cinchona bark in Peru and Bolivia are of special importance; such bark yields about 4 to 5 per cent. of sulphate of quinine.—*Chem. Zeit.*, xv. 735.

[1] Grimaux and Arnold, *Compt. Rend.*, cxii. 774. When a solution of cupreine in methyl alcohol is boiled for several hours under an upright condenser, with the theoretical quantity of sodium and excess of methyl iodide, a mixture of two iodomethylates was obtained, having all the characters of the compounds resulting from the similar treatment of quinine. By substituting methyl chloride for the iodide, and operating in a sealed tube at 100°, a base was formed, the sulphate of which had all the chemical and physical characters of quinine sulphate, the following reaction having probably occurred :—

$$\underset{\text{Sodium compound of cupreine.}}{C_{19}N_{21}N_2O.ONa} + CH_3Cl = NaCl + \underset{\text{Quinine.}}{C_{19}H_{21}N_2O.OCH_3}.$$

and the same compound can be obtained from an ethereal solution below 10°. But the resinoid mass left on the spontaneous evaporation of a solution of quinine in ether usually contains water in proportion corresponding to a monohydrate, and when the crystallised trihydrate is exposed in an exsiccator over sulphuric acid, it effloresces and loses its water more or less perfectly. At 20° C., over strong sulphuric acid, the trihydrate soon loses the whole of its water, but over equal measures of strong sulphuric acid and water a monohydrate results. At 15° C., in the open air, the trihydrate is unaltered, but at 20° C. it effloresces and loses 1 aqua, the residue having the composition of a dihydrate. Commercial quinine contains from 8 to 11 per cent. of water, and hence is approximately a dihydrate. The precipitate produced by ammonia at a low temperature in concentrated solutions of quinine sulphate is also usually a dihydrate. Hydrates of quinine containing 8 and 9 aqua have also been described. When the trihydrate is exposed to a temperature of 40° for a short time, and then to 60°, the whole of the water is driven off, and this change occurs rapidly at 100°. Resinoid quinine loses its water with some difficulty at 100° unless previously powdered, but at 120° becomes anhydrous very rapidly (see *Pharm. Jour.*, [3], xvi. 385, 897, 937).

Anhydrous quinine, obtained by drying the trihydrate over sulphuric acid and heating to 115°–120°, melts at 171·2°–172°, and that prepared by heating the benzene compound to 120° at 171·6°–172°.[1]

Quinine is odourless. When in solution or finely-divided it has an intense and purely bitter taste. It has valuable febrifuge properties, and is poisonous to frogs and other of the lower animals. It has decided antiseptic properties, retarding or arresting the alcoholic, lactic, butyric, amygdalous, and salicylous fermentations, but not the digestive action of pepsin.

Quinine is very sparingly soluble in water, according to J. Regnauld the solubility at 15° C. being 1 part in 2024. According to Sestini, however, the solubility of the anhydrous alkaloid in water is 1 in 1667 at 20° and 1 in 902 at 100° C., the trihydrate requiring 1428 and 773 parts of water at the same temperatures.

In dilute solutions of the fixed alkalies quinine is not more

[1] According to Hesse (*Annal.*, cclviii. 133) on prolonged heating of a solution of quinine in alcohol to 30° the alkaloid is converted into an isomeride for which he proposes the unsuitable name of homoquinine. This melts at 174·4°–175°, and is reconverted into quinine by prolonged heating with dilute sulphuric acid.

soluble than in pure water, but ammonia exercises considerably greater solvent action. Certain ammonium and calcium salts notably increase the solubility of quinine in aqueous liquids.

Quinine dissolves in about two parts of alcohol of 0·82 sp. gr., and is still more soluble in boiling alcohol. Crystallised quinine is stated to require from 22 to 30 parts of ether for solution, but freshly-precipitated quinine dissolves in little more than its own weight of ether. Quinine is also very soluble in chloroform (1 : 5), and dissolves readily in benzene,[1] petroleum spirit, and carbon disulphide.

Quinine exercises a powerful lævo-rotatory action on polarised light, the value of S_D being, according to Hesse $-145·2° - 0·657\ c$ at 15° C., for the solution of the hydrated alkaloid in 97 per cent. alcohol. In its salts, the optical activity of quinine has different values.

Quinine affords no visible colour or other reactions with strong acids. By cautiously dissolving quinine hydrate or sulphate in a mixture of equal volumes of concentrated nitric and sulphuric acids, amorphous dinitroquinine, $C_{20}H_{22}(NO_2)_2N_2O_2$, is produced, nearly insoluble in ether and forming uncrystallisable salts (E. H. Rennie, *Jour. Chem. Soc.*, xxxix. 469). The action of permanganate and chromic acid mixture on quinine is described on page 168.

Quinine is a powerful base, its solutions having a marked alkaline reaction to litmus and methyl-orange, and neutralising the strongest acids. It does not redden phenolphthaleïn.

Detection and Determination of Quinine.

The detection and estimation of quinine, when it occurs unmixed with other alkaloids or organic matter, is very readily effected, but the problem becomes more complex in the presence of other cinchona bases.

The following reactions are yielded by a solution of quinine in a moderate excess of dilute sulphuric acid :—

1. *Solutions of quinine in dilute sulphuric acid exhibit a* strong blue fluorescence. The effect is best observed in very dilute liquids, and is intensified by addition of excess of sulphuric acid. The hydrochloride and other haloid compounds of quinine (including the thiosulphate and cyanogen compounds) exhibit no fluorescence till excess of sulphuric acid is added, and the fluorescence of solutions of the sulphate is destroyed by very small quantities of hydrochloric acid or other chlorides, but can be again produced by adding excess of dilute sulphuric acid. Alcoholic

[1] Quinine is deposited from its solution in warm benzene in crystals containing $(C_{20}H_{24}N_2O_2)_2,C_6H_6,2aq$. (*Chem. News*, xlviii. 4).

solutions of quinine exhibit but little fluorescence, and solutions in the alkaloid in immiscible solvents none at all. Under favourable conditions, the fluorescence of quinine becomes an extremely delicate test for the presence of the alkaloid.[1] Fluorescence is also produced by quinidine, hydroquinine and hydroquinidine, and diquinicine, but not by quinamine, cinchonine or its isomers, cusconine, cupreine, or quinicine.

2. According to A. Weller (*Arch. d. Pharm.*, ccxxiv. 161), on adding chlorine-water to a strong solution of quinine the solution acquires a more or less intense red colour. Bromine-water is a preferable reagent, and on adding a few drops to a saturated solution of quinine hydrochloride a yellow precipitate is formed, which gradually disappears with formation of a rose-red coloration, changing to cherry-red. The colour disappears after a time, but can be reproduced by adding more bromine-water, and the reaction is more delicate and prompt if the quinine solution be previously gently warmed. Acids and excess of bromine-water prevent the reaction, which is also produced by quinidine, but not by cinchonine or cinchonidine.

3. If a solution of quinine, rendered as nearly neutral as possible, be treated first with chlorine or bromine, and then with excess of ammonia, a green substance called thalleioquin is produced, which in concentrated solutions forms a precipitate, and in more dilute a deep green liquid. When carefully applied, the test, which is due to Brande, is extremely delicate. Bromine is a more sensitive reagent than chlorine. The following is the best mode of applying the test:—To 10 c.c. of the solution of quinine add 3 c.c. of chlorine-water, or 0·5 c.c. of saturated bromine-water. Agitate well, and then add one drop of strong ammonia solution, or sufficient to render the liquid distinctly alkaline. If the proportion of quinine exceed about 1 per 1000 of solution, a green substance is precipitated, soluble in absolute

[1] The fluorescence of quinine is best observed by holding a test-tube filled with the solution in a vertical position before a window, when a bluish "bloom" will be perceived on observing the liquid from above against a dark background. Another plan is to make a thick streak of the solution on a piece of polished jet or black marble, or on a plate of glass smoked at the back, and to place the streaked surface in front of, and at right angles to, a well-lighted window.

The fluorescence of quinine solutions is not perceptible by gas-light, but may be brought out by burning a piece of magnesium ribbon in the proper position. The use of blue glass, which transmits the ultra-violet rays which produce the fluorescence of quinine, while excluding the less refrangible rays, is sometimes recommended. In this case the light transmitted by the glass should be concentrated by means of a lens.

alcohol, but insoluble in ether or chloroform. In more dilute liquids, even if the proportion of quinine does not exceed 1 in 20,000, a deep green coloration is produced. If the green ammoniacal solution be just neutralised with acid, a blue coloration is obtained, and on adding more acid a colour ranging from violet to red, but changing to green again on adding excess of ammonia.

H. Trimble has proposed to use this reaction for the approximate colorimetric determination of quinine. He dissolves 0·01 gramme of a quinine salt in 5 c.c. of fresh chlorine-water, and adds 10 c.c. of ammonia solution. The sample is treated in the same way, and the proportion of quinine ascertained from the relative volumes of the liquids when coloured equally intensely.

The thalleioquin reaction is also given by quinidine, cupreine, hydroquinine, hydroquinidine and diquinicine, but not by quinamine, or cinchonine and its isomers. It is prevented by morphine.

4. *If, after the addition of chlorine or bromine water, the* quinine solution be treated with a few drops of solution of potassium ferro- or ferri-cyanide, ammonia being *subsequently* added, a red coloration is produced instead of a green. The reaction is not so delicate as the thalleioquin test, but affords useful confirmatory evidence of the presence of quinine. A. Vogel modifies the test by adding bromine-water and potassium ferrocyanide to the solution to be tested, and then shaking with a fragment of marble, which, in presence of quinine, is at once covered with a red film. Strychnine, cinchonine, and caffeine do not give similar reactions.

5. On adding a fixed alkali, alkaline carbonate, or ammonia to a solution of a salt of quinine, a bulky white precipitate of the free alkaloid (more or less hydrated) is produced. The precipitate is very sparingly soluble in cold water or excess of these precipitants, with the exception of ammonia. The precipitate cannot be conveniently filtered off, washed, and weighed, as it is not wholly insoluble, and melts with very slight increase of temperature. Its state of hydration is also very uncertain. But, if the liquid containing the precipitated alkaloid be agitated with ether or chloroform, or a mixture of the two, the quinine passes readily and completely into solution, and may be obtained in the solid state by evaporating the solvent. The process is readily made quantitative by operating with care and repeating the agitation with the solvent, and the quinine may be weighed in the anhydrous state as $C_{20}H_{24}N_2O_2$, after being dried at 100° C. till constant in weight; or after exposure for fifteen or twenty minutes to a temperature of 120° C. The determination of quinine in this manner is capable of yielding very accurate results, and is of very extensive and rapid application.

6. When quinine exists in a free state, as it is obtained in process 5 by the evaporation of its solution in ether or chloroform, it may be determined by titration with standard acid. Each 1 c.c. of decinormal sulphuric acid ($=4·9$ grammes of H_2SO_4 per litre) corresponds to ·0324 gramme of anhydrous quinine. The process is conducted by dissolving the ether-residue in hot alcohol, adding as much water as can be used without causing precipitation, and titrating with decinormal acid. The indicator may be litmus, but methyl-orange or cochineal is decidedly preferable. Sharp readings are obtainable, but extreme care is necessary, owing to the very high combining-weight of quinine ($C_{20}H_{24}N_2O_2 = 324$). When methyl-orange is employed, the alkaloid may be conveniently used in ethereal solution, and in this case previous evaporation, as described under 5, is unnecessary, provided the ethereal solution be washed with water till the aqueous liquid gives no pink coloration with phenolphthaleïn.[1] The titration by standard acid, of course, merely indicates the total alkaloid present, in terms of quinine. The process furnishes a very useful check on the determination from the weight of the chloroform or ether-residue, and brings the alkaloid into a convenient form for further examination by one of the following processes:—

7. On adding tincture of iodine to a solution of acid sulphate of quinine in dilute alcohol, a curious compound is produced, called, after its discoverer, Herepathite, and having the formula $4C_{20}H_{24}N_2O_2,3H_2SO_4,2HI,I_4 + 3aq.$[2] This body, called also the iodo-sulphate of quinine or sulphate of iodo-quinine, is the type of a series of similar bodies formed by the action of iodine on the sulphates of the cinchona bases. Herepathite is but little soluble in cold water or dilute alcohol, and requires 1000 parts of hot water for solution; but it dissolves in boiling rectified spirit, and is deposited on cooling in tabular crystals, remarkable for their dichroism and their action on light,

[1] As quinine has no action on phenolphthaleïn, by the combined use of this indicator and methyl-orange it may be determined in its salts. Standard $\frac{N}{10}$ baryta-water is added to the aqueous liquid until the change of the liquid to yellow or brown shows that the free acid is neutralised. More baryta is then added slowly, with constant stirring, till the production of a pink colour shows that the whole of the acid in combination with the alkaloid is neutralised. Each 1 c.c. of additional $\frac{N}{10}$ alkali required represents 0·0324 gramme of quinine. The process has been used by Seaton and Richmond for determining quinine in medicines (*Analyst*, xv. 43).

[2] Herepathite may be readily prepared by dissolving the sulphate of quinine in 10 parts of proof spirit containing 5 per cent. of sulphuric acid, and adding an alcoholic solution of iodine as long as a black precipitate is produced. The precipitate is filtered off, washed, and recrystallised from hot alcohol.

a thin film of herepathite polarising the transmitted light as completely as the tourmaline. Herepathite is re-converted into sulphate of quinine by treatment with sulphurous acid, thiosulphates, sulphuretted hydrogen, and other reducing agents.

Iodosulphate of quinine possesses far less solubility than the corresponding compounds of the other cinchona bases.[1] This fact has been utilised by J. E. de Vrij for the determination of quinine (*Pharm. Jour.*, [3], vi. 461).

With the pure alkaloid the method is capable of yielding tolerably accurate results if a correction for solubility be applied, but investigations by A. Christensen, B. Y. Shimoyama and others have shown the process to have a limited practical value, as it is seriously invalidated by the presence of cinchonidine (*Pharm. Jour.*, [3], xii. 441, 1016; xvi. 205; xvii. 654). De Vrij's most recent method of operating is described on page 456.

E. B. Stuart (*Pharm. Jour.*, [3], xii. 1016) finds the herepathite reaction equally delicate with the thalleioquin test, and quite as easy of application. The salt of quinine should be dissolved in dilute alcohol, and dilute sulphuric acid, the presence of which is essential, added. Very dilute tincture of iodine is then added, drop by drop, with constant agitation, when the precipitate suddenly

[1] B. Y. Shimoyama (*Pharm. Jour.*, [3], xvi. 205) gives the following figures for the solubility of quinine herepathite in 90 per cent. alcohol at different temperatures :—

Temperature ; °C.	Alcohol without Acid.	Acidulated Alcohol.
15	1 in 869 parts.	1 in 255 parts.
16	„ 841 „	...
17	...	1 in 117 parts.
18	...	„ 101 „
20	1 in 738 parts.	...
25	„ 660 „	...
30	„ 638 „	...

The solubilities of the iodosulphates of the principal cinchona alkaloids in acidulated alcohol at 15° C. were found to be as follow :—

Alkaloid.	Solubility.	Percentage of Iodine.
Quinine herepathite, .	1 in 255 parts.	32·37
Cinchonidine, . .	„ 92 „	53·68
Quinidine, . . .	„ 61 „	42·70
Cinchonine, . .	„ 42 „	24·90

appears and quickly subsides. Precipitation as herepathite may be used with advantage for separating quinine from morphine even when the relative proportions are as 1 : 1000.

8. In 1862, André (*Jour. de Pharm.*, xli. 341) described a method of estimating quinine and separating it from other cinchona bases by precipitation as the chromate, which is stated to be soluble in 160 parts of boiling water or 2400 of water at 15° C., and not liable to alteration by light or on boiling an aqueous solution. A method of assaying quinine, based on the same principle, was described in 1887 by J. E. de Vrij (*Arch. Pharm.*, [3], xxiv. 1073), who attributes to the precipitate the formula $(C_{20}H_{24}N_2O_2)_2H_2CrO_4$, and states that it is soluble in 2733 parts of water at 12°, or 2000 parts at 16° C. He directs that 5 grammes of quinine sulphate should be dissolved in 500 c.c. of hot water, and a solution of 1·2 gramme of neutral potassium chromate in a little warm water added. After standing in the cold for twelve hours, the precipitate is filtered off, washed with cold water, and weighed after drying in the air. A correction of 0·005 gramme is made for every 10 c.c. of mother-liquor and wash water. This method has been severely criticised by O. Hesse (*Pharm. Jour.*, [3], xvii. 585, 665; xviii. 582), who finds the precipitated chromate of quinine to contain 2 aqua, which fact accounts for some experimenters, working according to de Vrij's directions, having obtained an apparent excess of quinine. On the other hand, cinchonidine and hydroquinine are in part thrown down with the quinine, which renders the method inapplicable for separating quinine from its most constant associates.

Quinine is distinguished :—

1. From cinchonine, *a*, by its fluorescence; *b*, its lævorotation; *c*, the thalleioquin test; *d*, the crystallisation of the sulphate; *e*, its solubility in ether; *f*, its solubility in ammonia; *g*, the sparing solubility of the iodosulphate.

2. From cinchonidine by most of the above reactions, except *b*, and less sharply than cinchonine by those tests depending on relative solubility (*d*, *e*, *f*, *g*).

3. From quinidine by *b*, *d*, *f*, *g*; also by (*h*) yielding no precipitate with potassium iodide, and (*i*) the insolubility of the sulphate in chloroform.

4. From quinamine by *b*, *e*; *j*, precipitation as tartrate; and *k*, the sparing solubility of the sulphate.

5. From cupreine by *a*, and (*l*) the insolubility of the precipitated alkaloid in excess of soda.

Methods for the separation of quinine from the associated *cinchona bases* are given on pages 411, 453, *et seq.*

The separation of quinine from *morphine* may be effected, as already stated (page 405), by precipitation as herepathite; also by treating the free alkaloids with chloroform or ether, which leaves the morphine undissolved.

From *strychnine*, quinine may be separated as indicated under "Easton's syrup" (page 377).

SALTS OF QUININE.

Quinine is a strong base, completely neutralising acids, and forming crystallisable salts having no reaction on litmus or methyl-orange. These salts react with phenolphthaleïn as if the acid were in an uncombined state. Quinine also forms a series of acid salts, of which the acid sulphate of quinine is the type.

Several of the salts of quinine are official in the *Pharmacopœia*, and others are extensively used in medicine.

Quinine Sulphate. Diquinic sulphate. $(C_{20}H_{24}N_2O_2)_2H_2SO_4$. This important salt, sometimes called "disulphate" or "basic sulphate" of quinine, forms, in the hydrated state, the ordinary medicinal sulphate of quinine of commerce.

Sulphate of quinine is usually met with in exceedingly light scales, or long, flexible filiform needles,[1] having a nacreous aspect and a pure and intensely bitter taste.

The crystallised sulphate of quinine of commerce usually contains about 14·5 per cent. of water, a proportion which corresponds closely to a 7-atom hydrate, which requires 14·45 per cent. According to some authorities, however, the wholly uneffloresced crystals contain 8 aqua, or at any rate 7½ aqua.[2] H. B. Parsons

[1] Chemically pure quinine sulphate, free from hydroquinine, crystallises in heavy needles resembling sulphate of zinc. The light character of the commercial salt is chiefly due to the presence of small admixtures of the sulphates of hydroquinine and cinchonidine, and possibly of hydrocinchonidine and homocinchonidine. One per cent. of cinchonidine is sufficient to produce the light silky appearance, and this persists with a larger proportion. "A few years ago, when the bark of Remijia, which contains no cinchonidine, was first treated, the latter alkaloid was added, as the pure solutions yielded large brilliant needles unfamiliar in commerce; for the same reason the bark of cuprea was never treated, except by being mixed with other barks." The sulphates of the bases of the cinchonidine group can be separated from quinine sulphate without interfering with its light form when there is a sufficient amount of hydroquinine present. According to Carles, an addition of 4 grammes of ammonium sulphate to 1 litre of a hot saturated solution of quinine sulphate causes the latter salt to crystallise on cooling in a very voluminous form.

[2] The *British Pharmacopœia* of 1885 gives the formula of crystallised quinine sulphate as $(B_2H_2SO_4)_215H_2O$, which corresponds to 7½ aqua. The freshly prepared salt is stated to lose 15·2 per cent. of water when dried at the temperature of boiling water.

(*Proc. Amer. Pharm.*, xxxii. 457) has published the results of drying for three hours, at 100°, 1015 samples of quinine sulphate (taken from tins holding 100 ounces each, and not previously opened) of American, German, and Italian manufacture. The average loss of water was 13·84 per cent., the highest average from any one maker being 14·36 per cent. A. J. Cownley (*Pharm. Jour.*, [3], xvi. 797) found the water in thirty-seven samples of commercial quinine sulphate examined during the two years prior to 1886 to range from 8·10 to 16·12 per cent. D. Hooper states that the water ranges from 5 to 18 per cent. Hesse (*Ber.*, xiii. 1517) states that pure crystallised quinine sulphate, which has not effloresced, contains $8H_2O$, or 16·17 per cent. of water. Cinchonidine sulphate, on the contrary, crystallises with $6H_2O$, or 13·7 per cent. Hence, if a sample of quinine sulphate be dry and quite free from efflorescence, the proportion of water is an indication of its purity.

Crystallised quinine sulphate is rendered perfectly anhydrous by exposure to a temperature of 100° C. If a higher temperature be employed for its dehydration, there is a danger of some of the alkaloid undergoing conversion into quinicine (see page 434). If the anhydrous sulphate of quinine be exposed to moist air, it rapidly absorbs from 4·8 to 5 per cent. of water, a proportion which corresponds to the formula $B_2H_2SO_4+2H_2O$.[1] On the other hand, the crystallised salt rapidly loses water on exposure to air, until it acquires the composition of the 2-atom hydrate. The same quantity of water is retained when the crystallised salt is dried over sulphuric acid, or crystallised from strong alcohol.

Quinine sulphate requires 750 parts of cold water for solution, but dissolves in about 30 parts of water at 100° C. It is far less soluble in water containing sulphate of magnesium, sodium, or ammonium than in pure water. In a strong solution of Rochelle salt, quinine sulphate is so little soluble that the alkaloid can scarcely be detected by the fluorescence or thalleioquin test. On the other hand, the solubility of sulphate of quinine in water is increased by the presence of ammonium chloride, or of potassium nitrate or chlorate.

In alcohol, quinine sulphate dissolves more readily than in water, requiring only 7 or 8 parts at a boiling temperature, but it is much less soluble in cold spirit (see "Tincture of Quinine," page 423). Quinine sulphate dissolves in about 24 parts of cold glycerin, the solution being precipitated by addition of water. Crystallised quinine sulphate is not soluble in fixed oils,

[1] H. P. Parsons recommends the official adoption of this hydrate as a definite and stable form of quinine sulphate.

ether, chloroform, or petroleum spirit. (It is said to dissolve in benzene.) In the anhydrous state, 1 part of quinine sulphate is soluble in about 1000 parts of chloroform (see page 416).

In dilute sulphuric acid, quinine sulphate is readily soluble, owing to the formation of *acid sulphate of quinine*, $C_{20}H_{24}N_2O_2,H_2SO_4$. This salt is readily obtainable in crystals containing $7H_2O$. The crystallised salt loses 6 aqua in the exsiccator, and becomes anhydrous at 100° C. When heated to about 135° C. it melts, and is converted into the corresponding compound of quinicine (see page 434). Acid sulphate of quinine dissolves in 11 parts of cold water, and more readily in hot water or in alcohol to strongly fluorescent solutions.

From a solution of quinine in excess of dilute sulphuric acid, an *acid sulphate* may be obtained, having the composition $C_{20}H_{24}N_2O_2,2H_2SO_4, + 7H_2O$ ($= C_{20}H_{24}N_2O_2,H_2SO_4 + H_2SO_4 + 7H_2O$).

Normal quinine sulphate has a specific rotation in alcoholic solution of $S_D = 191{\cdot}5°$, calculated for the anhydrous salt. Excess of acid increases the rotatory power. When dissolved in water acidulated with hydrochloric acid, the value of S_D at 15° is 233·75° (Hesse).

Sulphate of quinine is largely employed as a febrifuge and tonic, the official dose ranging from 1 to 10 grains. It has marked antiseptic properties.

The fluorescence of sulphate of quinine is considered on page 400; its reaction with iodine on page 403; and with the thalleioquin test on page 401.

Examination of Commercial Quinine Sulphate.

The salts of quinine, except the tannate (page 420), can all be examined by the following methods applicable to the sulphate of quinine, provided they are first treated with 10 parts of boiling water and their own weight of sodium sulphate. The sulphate of quinine which deposits on cooling and the mother-liquor obtained can then be examined in the usual way.

Commercial sulphate of quinine was formerly subject to adulterations of a very gross character. Among the bodies employed to sophisticate it are said to have been starch, gum, stearin, salicin, phloridzin, sugars, sulphate of magnesium, sulphate of sodium, chalk, asbestos, boric acid, &c. Some of these additions are apocryphal and the majority are certainly obsolete.

Mineral additions would be readily recognised on igniting the sample, which, when pure, will leave no sensible ash. Starch, chalk, stearin, and boric acid would remain insoluble on treating the substance with cold dilute sulphuric acid, and gum would be

precipitated on adding excess of alcohol to the solution thus obtained. Soluble impurities generally may be detected and estimated by dissolving the sample in hot water and adding excess of baryta water. The alkaloid is then removed by agitation with ether. After removing the ethereal layer, a stream of carbonic acid is passed through the aqueous liquid to precipitate the excess of baryta, and the whole well boiled and filtered. Sulphate and carbonate of barium will be left insoluble, and the filtrate will contain any sugar or other soluble impurity present in the original sample, and the observation of the weight of the residue left on evaporation will allow of a determination of the amount. In presence of *sugar* the liquid will exert a dextro-rotatory action, and in presence of *salicin* a lævo-rotatory action on polarised light.

Treatment of the original solid sample with concentrated sulphuric acid, attended by gentle warming, will suffice for the qualitative detection of some impurities. Sugar and mannite will become charred, while salicin developes a striking red colour. Good commercial quinine sulphate dissolves with faint yellow colour in strong sulphuric acid, and the tint is not deepened on warming gently.

Similar general impurities may be rapidly tested for by a test devised by Hesse, and described on page 417. *Salicin*, if present in greater proportion than 1 per cent., may be detected by this test. The residue insoluble in the chloroform-mixture will be coloured deep red by concentrated sulphuric acid, and will reduce Fehling's solution after boiling with dilute sulphuric acid. The reaction with strong sulphuric acid will be produced by the original sample if the proportion of salicin be considerable. Smaller proportions of salicin may be detected in the filtrate from the precipitate produced by adding baryta to the aqueous solution of the sample. Another test for salicin is to dissolve 0·25 gramme of the sample in 4 c.c. of water and 4 drops of concentrated hydrochloric acid. If salicin be present, on boiling the liquid for some minutes a white turbidity will be produced, due to the formation of saliretin.

Sulphate of quinine has occasionally been largely adulterated with or entirely substituted by the hydrochloride of cinchonine. This fraud is recognisable by testing for chlorides with nitric acid and nitrate of silver, and for cinchonine as described on page 413.

The most common impurity of commercial sulphate of quinine is an admixture of one or more of the sulphates of *other cinchona alkaloids*, especially *cinchonidine*. This admixture is often purely accidental, owing to imperfect separation of the other alkaloids during manufacture, but is no doubt sometimes provided for and

secured by suitable arrangements of the manufacturing operations, while occasionally an intentional admixture of other alkaloids has occurred.

Manufacturers of quinine sulphate produce at least four qualities of the article. (1) The pure salt or "heavy sulphate," of which the use has been hitherto extremely limited, chiefly on account of its unfamiliarity to the members of the medical profession; (2 and 3) products satisfying the requirements of the *German* and *Dutch Pharmacopœias*; and (4) products satisfying others than the above-mentioned pharmacopœias, and containing from 4 to 6 per cent. of sulphate of cinchonidine. Other products may have a certain commercial importance, but have no "legal status" in civilised countries.

The best samples of commercial quinine sulphate are seldom free from cinchonidine, but contain not more than 2 or 3 per cent.; whilst other kinds contain from 5 to 10, and even 20 per cent. of cinchonidine sulphate, and on one occasion B. H. Paul found 60 per cent.

F. W. Fletcher (1882) states that quinine of English manufacture is usually practically free from cinchonidine, but that certain foreign brands always contain from 10 to 15 per cent., in one case the proportion exceeding 25 per cent. A. J. Cownley has published determinations of cinchonidine made by a reliable process, and finds the proportion to range from *nil* to 13·9 per cent., the next largest amount being 9·0 per cent. More recently (1889), Paul and Cownley (*Pharm. Jour.*, [3], xix. 665) found the cinchonidine sulphate present in twenty-three typical samples of quinine sulphate, representing all the different makers, to range from *nil* (in two instances) to 12·34 per cent. In fourteen out of the twenty-three the proportion of impurity was less than 6 per cent. The two samples which were wholly free from cinchonidine were probably manufactured from cuprea bark, which is characterised by the absence of cinchonidine, and in one instance this conjecture was confirmed by the detection of a trace of *cupreine* in the sample. In addition, *hydroquinine* is a very constant impurity in quinine sulphate, a very notable proportion being sometimes present, and, according to Hesse, *hydrocinchonidine* and *homocinchonidine* may also be met with in quinine from certain sources. The presence of even 1 per cent. of *cinchonine* or *quinidine* in quinine sulphate is far more likely to be intentional than due merely to accident or careless manufacture, but these alkaloids are apt to be met as accidental impurities in quinine hydrochloride.

The detection and estimation of foreign alkaloids in commercial

sulphate of quinine has received much attention, and considerable ingenuity has been exercised in the solution of this somewhat difficult problem.

The recognised methods of testing commercial quinine sulphate for admixtures of other alkaloids are, for the most part, based on the removal of the greater part of the quinine as a sparingly soluble sulphate, and the distinction of the remaining quinine from its associates by its greater solubility in ether and its solubility in excess of ammonia. A great variety of tests based on these principles have been devised, especially for recognition and estimation of cinchonidine, the detection and determination of the other alkaloids when present in notable proportion presenting comparatively little difficulty.

The separation of small proportions of *cinchonidine* from quinine is particularly troublesome, and formerly any considerable proportions of the admixture must have escaped recognition. B. H. Paul (*Pharm. Jour.*, [3], vii. 653) has shown that when the test for quinine sulphate prescribed in the *British Pharmacopœia* of 1867 is rigidly adhered to, it is difficult to detect an admixture of 20 per cent. of the cinchonidine salt. By reducing the volume of ether used, any impurity in excess of 10 per cent. may be detected, but less than this proportion escapes recognition, owing to the property possessed by quinine of increasing the solubility of cinchonidine in ether, or at any rate of preventing the latter from separating in a crystalline state. Hence, for the detection of small proportions of cinchonidine, it is necessary first to separate the greater part of the quinine. This may be done by utilising the fact that quinine sulphate requires about 750 parts of cold water for solution, while cinchonidine sulphate is soluble in 100 parts. This principle was originally employed by Kerner, but its application has been modified and improved in several respects by Paul (*Pharm. Jour.*, [3], vii. 653; xvii. 645), and Hesse (*Pharm. Jour.*, [3], xvii. 975). But cold water does not completely dissolve cinchonidine sulphate from commercial quinine sulphate, according to Hesse, because of its existence in the form of a double sulphate of the two alkaloids. This compound is decomposed or disintegrated by hot water, even if the quantity of liquid be insufficient for its solution, the cinchonidine salt passing almost wholly into solution, while the quinine sulphate is for the most part undissolved. On the point whether it is better to treat the sample with water at 60° or to 100° C., authorities are at variance. Hesse considers that at a boiling heat more of the quinine sulphate will pass into solution, and hence there will be a greater tendency to the re-formation of the double salt when crystallisation takes

place. Kerner and Weller also recommend the use of water at 60°. E. Jungfleisch (*Jour. Pharm. et Chim.*, [5], xv. 5; *Pharm. Jour.*, [3], xvii. 585) gives the preference to a boiling temperature, and points out the tendency to erratic results if less heat be employed. Paul (*Pharm. Jour.*, [3], xvii. 595) considers that the best results can only be obtained by using nearly sufficient water to effect the complete solution of the quinine sulphate at the boiling-point.

The mode of operating recommended by Hesse is to take 1 gramme of quinine sulphate previously dried at 100°, shake it with 20 c.c. of water at 60° C., filter after cooling, and agitate 5 c.c. of the filtrate in a narrow tube with 1 c.c. of ether and 5 drops of ammonia (sp. gr. 0·96). The clear ethereal solution thus obtained should not deposit crystals on standing. If, on leaving the tube at rest and in a closed condition for two hours, the ethereal stratum be found free from crystals, the sample may be considered pure; but if it contain more than 0·25 per cent. of cinchonine sulphate, 0·5 of quinidine sulphate, or 1·0 per cent. of cinchonidine or homocinchonidine sulphate, a distinct separation of crystals will occur. The last two impurities appear granular, while crystals of cinchonine and quinidine form concentric groups of delicate needles. If the proportion of cinchonidine be as high as 3 per cent., the separation of crystals will occur immediately, or within three minutes; 2 per cent. will show in about ten minutes; while with less than 1 per cent. no separation will occur even after twelve hours.[1] To detect smaller proportions of these alkaloids, the cork of the tube should be replaced by a loose plug of cotton-wool, so that the ether may gradually evaporate. On examining the residue with a lens it will appear distinctly crystalline if ½ per cent. of cinchonidine or homocinchonidine sulphate be present, and a mere trace will be recognisable by the presence of a few crystals in the amorphous mass of quinine. 0·5 per cent. of cinchonine sulphate, or 1·0 per cent. of quinidine sulphate, will cause an almost immediate separation of crystals from the ether. Their presence is far more likely to be intentional than merely accidental or due to careless manufacture.

The *British Pharmacopœia* of 1885 gives the following methods of testing commercial sulphate of quinine for accompanying

[1] A deposit of cinchonidine is recognised by the capillary rising of the precipitate beyond the ethereal layer immediately after shaking the solution. With a large proportion of cinchonidine a white chalky ring appears at the line of contact of the two liquids.

loids.[1] The salt "should not contain much more than 5 per
. of other cinchona alkaloids":—

. *Test for Cinchonidine and Cinchonine.* Heat 100 grains of sample in 5 or 6 ounces of boiling water, with 3 or 4 drops of te sulphuric acid.[2] Set the solution aside until cold. Separate iltration the purified crystals of quinine sulphate which cryse out. To the filtrate, which should nearly fill a bottle or , add ether, shaking occasionally, until a distinct layer of r remains undissolved. Then add ammonia in very slight ss, and shake thoroughly, so that the quinine at first pretated shall be redissolved by the ether. Close the flask, and w it to stand for some hours, and then remove, with a pipette, supernatant, clear, ethereal layer which should occupy the neck he flask. Agitate the residual aqueous liquid and the separated tals of alkaloid once or twice with a *very little* ether. Collect separated alkaloid on a tared filter, wash it with a *little* ether, at 100° C., and weigh. Four parts of the product represent of crystallised sulphate of cinchonine or cinchonidine in the ple.

. *Test for Cupreine.* Shake the crystallised sulphate of quinine ined in Test *a* with 1 fluid ounce of ether and ½ fluid ounce of ionia (sp. gr. 0·959), separate the ethereal solution, and add to e ethereal solution and washings obtained in Test *a*. Shake united ethereal liquid with 1½ fluid ounce of caustic soda tion (10 per cent.), adding water if any solid matter separates. arate the ethereal layer, agitate the aqueous liquid with more r, and separate as before. Heat the aqueous liquid to boiling, exactly neutralise it with dilute sulphuric acid. Allow the tion to cool, separate any crystalline cupreine sulphate by a d filter, wash with a little cold water, dry and weigh.

. *Test for Quinidine.* Recrystallise 50 grains of the sample as

[1] The *French Codex* of 1884, making use of Kerner's method of analysis, ribes that 5 c.c. of a mother-liquor obtained at 15° C., after treatment of amme of the officinal salt with 10 c.c. of luke-warm water, shall remain ctly limpid for 24 hours after the addition of 7 c.c. of a solution of onia of 0·96 specific gravity. The manufacturers considered these regula severe. However, the new *Austrian Pharmacopœia* prescribes the use of . of ammonia, which is only slightly less severe a test; and the pharmaias of Russia, Finland, Sweden, the United States, and Japan have ted nearly the same test. The *Dutch Pharmacopœia* has reduced the nt of ammonia to 5 c.c., and the *German Pharmacopœia* of 1890 to 4 c.c.

[2] This addition of sulphuric acid is objectionable, as tending to increase the ility of the quinine sulphate and diminish the delicacy of the test. It d be better to direct the addition of just sufficient acid to render the ion faintly acid to litmus.

just described in Test *a*, and to the filtrate add a strong solution of potassium iodide, and a little rectified spirit to prevent the precipitation of the hydriodides of amorphous bases. Collect the precipitate of quinidine hydriodide, wash it with a little cold water, dry at 100°, and weigh. "The weight represents about an equal weight of crystallised sulphate of quinidine."

The foregoing tests are, of course, not intended for the detection and estimation of minute traces of accompanying alkaloids in quinine sulphate. Cinchonidine has about one-fourth the potency of quinine, and hence the therapeutic value of the preparation is not so greatly affected by a small admixture as is the commercial value.

B. H. Paul (*Pharm. Jour.*, [3], xvii. 647) points out that the delicacy of the test would be much increased by evaporating the filtered aqueous solution to about one-fifth of its volume before shaking with ether and ammonia.[1] Operating in this manner, as small a proportion as 1 per cent. of cinchonidine sulphate can be detected with certainty, even when only 10 grains of the sample is employed, provided that the closed tube (employed with small quantities instead of a flask) be allowed to stand for at least twelve hours for the formation of the crystals. De Vrij (*Chem. Centr.*, 1885, 968) has suggested the addition of sufficient sulphuric acid to convert the bases into acid salts before separating them by fractional solution and crystallisation. Hesse (*Pharm. Jour.*, [3], xvii. 486), who expresses a high opinion of this method if carefully performed, recommends the following mode of operating:—5 grammes weight of the sample is dissolved by the aid of heat in 12 c.c. of normal sulphuric acid (49 grammes H_2SO_4 per litre) contained in a small porcelain basin, and the solution poured into a funnel closed at the bottom,[2] in which it is allowed to cool. At the end of two hours crystallisation is complete, the stopper is removed, and the mother-liquor allowed to drain away as completely as possible, its removal being assisted by suction. The upper portion of the crystals is then pressed down with a glass rod and washed with 3 c.c. of cold water, added drop by drop while the suction is kept up. The whole solution is then mixed with 16 c.c. of ether (sp. gr. 0·721 to 0·728) and shaken up.[3] Three c.c. of ammonia (sp.

[1] In a later paper (*Pharm. Jour.*, [3], xix. 665) Paul and Cownley recommend that the solution should be concentrated to about 1 fluid drachm (3½ c.c.), and the deposited crystals separated before treatment with ammonia and ether.

[2] This may be conveniently effected by a glass rod introduced from above, and having the lower end covered with a short length of india-rubber tubing. The same rod can be afterwards used for pressing down the crystals.

[3] If the sample contain more than 10 per cent. of cinchonidine the volume of ether must be increased.

gr. 0·960) is next added, and the whole well shaken again. After standing one day the ether is removed with a pipette, and the crystals which have separated are collected on a filter and washed with water saturated with ether. The filter is then placed on an absorbent surface, the crystals again washed with some ether, and dried at 100°. These crystals are not pure cinchonidine, but a compound of quinine and cinchonidine, having the composition $C_{20}H_{24}N_2O_2, 2C_{19}H_{22}N_2O$. There is always a certain amount of adhering quinine, especially when the proportion of cinchonidine in the sample is very small, and hence Hesse recommends that the weight obtained should be multiplied by 0·62, instead of by 0·645, which is the calculated factor for the above formula.[1]

B. H. Paul (*Pharm. Jour.*, [3], xvii. 555) strongly objects to the acid sulphate test, on the ground that the crystals of acid sulphate are not free from cinchonidine, while the amount of quinine retained in solution is so much increased as to interfere with the subsequent crystallisation of the cinchonidine from ether.

Conversion of quinine into and crystallisation as the acid sulphate effects a separation of *hydroquinine*, which remains in the mother-liquor, while repeated recrystallisation of the neutral sulphate fails to effect this (compare page 424).

A method of assaying quinine sulphate for cinchonidine, based upon the optical rotation of the solution, has been recommended by several eminent authorities and is equally distrusted by others. Oudemans was among the first to experiment in this direction, and Hesse proposed a definite process of assay, based on the rotation of the sulphate. Koppeschaar proposed to employ the tartrates by preference, while R. H. Davies operated on the sulphates. De Vrij has strongly recommended the optical method of examination, giving preference to the tartrates. Jungfleisch and Paul and Cownley have expressed strong distrust of the optical method, considering it manifestly impracticable to determine proportions of 1 and 1½ per cent. of cinchonidine in quinine sulphate containing even minute proportions of the cinchonine and quinidine salts; and D. Howard states that no published method gives the mixed tartrates of quinine and cinchonidine sufficiently pure to render the polarimetric assay absolutely reliable. Hesse has modified his former high opinion of the method, and points out that it is invalidated by the presence of hydroquinine, which is invariably present in commercial quinine sulphate, and is not separated by converting the bases into tartrates.

[1] Hesse's test-experiments on mixtures of pure quinine and cinchonidine sulphates in known proportions justify this empirical factor.

The presence of 1 per cent. of hydroquinine sulphate reduces the rotation to the same extent as 0·42 per cent. of the cinchonidine salt, and its presence accounts for the excessive and discordant figures for cinchonidine often obtained by those who rely on the optical method of assay. Hydroquinine cannot be perfectly separated from quinine even by repeated recrystallisations of the neutral sulphate, but it can be completely got rid of by converting the alkaloid into the acid sulphate and recrystallising this from water or alcohol, when the hydroquinine remains in the mother-liquor (compare page 424).

For the optical assay, Koppeschaar (*Zeitsch. Anal. Chem.*, xxiv. 362) recommends that the quinine and cinchonidine should be converted into tartrates by precipitating the neutral solution with Rochelle salt, and the precipitate washed with a little cold water and dried at 125°–130° C.; 0·400 gramme of the dry product is then dissolved in 3 c.c. of normal hydrochloric acid, and the solution diluted with water at 15° C. to a volume of 20 c.c. The solution is placed in a jacketed tube kept at 15° C., and the rotatory power observed by a polarimeter employing monochromatic (sodium) light. From the angular rotation the specific rotatory power of the tartrate is then calculated by the formula $S = \frac{100a}{2l}$; where S is the specific and a the angular rotation, and l the length of the tube in decimetres. From the figure thus obtained, the percentage of quinine tartrate, x, in the mixed tartrate may be ascertained by the following (Koppeschaar's) formula:—

$$x = \frac{100(S - 137{\cdot}67)}{82{\cdot}4}$$

Each 1° of diminution in the specific rotation below 220·07° corresponds to about 1·2 per cent. of cinchonidine tartrate in the mixed tartrates. The angular rotation is diminished by 0·077° only by the presence of 1 per cent. of cinchonidine tartrate. Notwithstanding the extreme accuracy of observation necessary, Hooper (*Pharm. Jour.*, [3], xvii. 61) has found the optical determination of quinine in the mixed tartrates to give very satisfactory results. Hesse found the specific rotation of quinine, hydroquinine, and cinchonidine tartrates, for Oudemans' concentration B, to be respectively, −212·5°, −176·9°, and −132·0°.

For the detection of *cinchonine*[1] or *quinidine* in quinine sulphate, Hesse proposes to dry the salt at 100° C., and agitate 1 gramme with 15 c.c. of chloroform free from alcohol. The liquid is passed

[1] According to Laborde (*Pharm. Jour.*, [3], xiii. 684) the presence of cinchonine materially alters the physiological effects of quinine salts.

through a small filter. If 10 c.c., on evaporation at a gentle heat, leave an amorphous residue weighing more than ·035 gramme, cinchonine or quinidine sulphate is certainly present. If the residue be crystalline and less than the above weight, it may be tested for the foreign alkaloids by heating it with 5 c.c. of water, adding ½ gramme of potassium sodium tartrate, cooling, filtering from the precipitated quinine and cinchonidine tartrates, and mixing the filtrate with an equal volume of ammonia. If quinidine or cinchonine be present, a precipitate will be formed, and may be further examined by agitation with ether (see page 412), or by treatment with iodide of potassium (see page 413). Sulphate of cinchonidine, if present, will remain undissolved by the chloroform, but will swell up into very bulky needles, which suck up the chloroform like a sponge and do not yield it again without pressure.

L. Schäfer (*Arch. Pharm.*, [3], xxv. 64, 1033) has described a method of testing commercial quinine sulphate, based upon the precipitation of the boiling aqueous solution by neutral potassium oxalate. After cooling and filtering, the filtrate is tested by addition of caustic soda.

O. Schlickum (*Arch. Pharm.*, [3], xxv. 128) has investigated De Vrij's chromate method (page 405), and finds it applicable, under certain conditions, to the examination of quinine sulphate. On precipitating a solution of this or other neutral quinine salt with neutral potassium chromate, and filtering after four or more hours, the filtrate remains clear on addition of soda, if the quinine salt was pure. In presence of ½ per cent. of cinchonine sulphate, or 1 per cent. of the quinidine or cinchonidine salt, a turbidity is produced at once or after a time.

A test for the purity of quinine sulphate, devised by Hesse and adopted by the *German Pharmacopœia*, consists in heating 1 gramme of the sample for a short time to 40°–50° C., in 7 c.c. of a mixture of 2 volumes of chloroform and 1 of absolute alcohol. If the sample be pure it is completely dissolved, and the solution remains quite clear on cooling. Sulphates of other cinchona bases and various organic and inorganic impurities remain insoluble (compare page 409).

A somewhat similar test has been described by E. Hirschsohn, according to which 0·2 gramme of the quinine sulphate should be briskly agitated with 5 c.c. of a mixture of 30 parts of petroleum ether of 0·680 sp. gr. with 70 parts of chloroform. The liquid is filtered, and diluted with three or four times its volume of petroleum ether, when an admixture of 0·1 per cent. of sulphates of other cinchona bases will give rise to a turbidity or precipitate.

For the detection of *amorphous alkaloid* in commercial quinine

sulphate, De Vrij recommends the following method :—The sample is dissolved in dilute acid, and shaken with ammonia and ether for estimation of total alkaloid. Sufficient decinormal oxalic acid is added to the ether-residue to convert the alkaloid into neutral oxalate, and the liquid is evaporated at a steam-heat and the residue thoroughly dried in the water-bath. It is then dissolved in chloroform, and the liquid filtered if necessary. The clear solution is next treated in a test-tube with a few drops of water, when crystals of oxalate of quinine will appear in the chloroform. If the sample were pure the aqueous layer will remain clear and uncoloured, but if amorphous alkaloid be present it will be dissolved by the water and colour it yellow.

Quinine Hydrochloride. Hydrochlorate of quinine. B,HCl. This salt forms long asbestos-like prisms containing 2 aqua, which become anhydrous at 120° C. without previously melting. The dehydrated salt fuses at 158°–160° without change, and is not converted into quinicine, as stated by Pasteur (Hesse). If an aqueous solution of quinine hydrochloride saturated at 15° C. be allowed to stand for some time at about 0° C., large octahedral crystals containing 3 aqua separate out. Quinine hydrochloride is soluble in about 40 parts of cold water, and very soluble in hot water and in alcohol.

Quinine hydrochloride has been frequently substituted of late years for the sparingly soluble sulphate. Thus it is used in making the Tincture of Quinine, B.P. The hydrochloride is the more expensive salt, owing to the increased difficulty of crystallising and the high percentage of quinine contained in it (84·2 per cent., against 73·5 in the crystallised sulphate).

Quinine hydrochloride is prepared by reacting on the sulphate with chloride of barium.[1] Hence it is apt to contain either undecomposed sulphate of quinine, or else barium chloride. The latter impurity is, of course, very objectionable.

Quinine hydrochloride may be assayed in much the same manner as the sulphate (see page 408 *et seq.*). The B.P. test for quinine sulphate is applicable to the examination of the hydrochloride, if the sample be previously dissolved in ten times its weight of boiling distilled water, together with its own weight of crystallised sodium sulphate. The crystals of quinine sulphate which are deposited, and the filtrate from them, can then be examined as

[1] The *acid hydrochloride*, BH_2Cl_2, is obtained by precipitating the acid sulphate of quinine by barium chloride. It forms groups of concentric needles, which can be dried without change at 110°, and are soluble in an equal weight of water. It also separates as a gelatinous mass, which becomes crystalline on gentle warming.

described on page 412 *et seq.* The hydrochloride of quinine is more likely to be contaminated with the similar salts of cinchonine and quinidine than with the hydrochlorides of cinchonidine and homocinchonidine.

Quinine hydrochloride has on several occasions been accidentally mixed with or replaced by the corresponding salt of *morphine.* The impurity may be detected by warming the salt with dilute nitric acid, which acquires a yellow or red colour if morphine be present; or the salt may be placed in a porcelain crucible and moistened with very neutral ferric chloride, which will produce a green or blue colour if morphia be present. The production of a blue colour with mixed solutions of ferric chloride and potassium ferricyanide (page 317) is also well adapted for the detection and approximate estimation of morphine in presence of cinchona bases. Lastly, the aqueous solution of the salt may be treated with ammonia and agitated with a small quantity of ether, when any morphine (or cinchonine) will remain undissolved.

Quinine Hydrobromide, $BHBr+H_2O$, is prepared by mixing equivalent quantities of quinine sulphate and potassium bromide with their own weight of water, adding three or four parts of strong alcohol, filtering from the precipitated potassium sulphate, and crystallising the quinine hydrobromide from the filtrate. The salt forms silky needles, soluble in 16 parts of water to a solution said to be fluorescent (?).

Quinine Carbonate, $B_2H_2CO_3+H_2O$, is obtained by passing carbon dioxide into water containing freshly precipitated quinine hydrate, and exposing the resultant solution to the air. It forms translucent needles, efflorescing rapidly in the air, decomposing at 110° C., and soluble in water or alcohol but insoluble in ether.

Quinine Chromate, $B_2H_2CrO_4+2H_2O$. The anhydrous salt rapidly re-absorbs 2 aqua on exposure to air. It is soluble in about 2000 parts of cold water, and has been recommended by de Vrij for the determination of quinine (page 405). It becomes anhydrous at 80°, and decomposes at a higher temperature.

Quinine Oxalate, $B_2H_2C_2O_4+6H_2O$, forms delicate needles soluble in about 900 parts of cold water. The oxalates of the other frequently occurring cinchona bases are comparatively easily soluble, and L. Schäfer has based on this fact a method of separating small proportions of these bases from quinine (page 417).

Quinine Valerate forms colourless rhomboidal plates, having a pearly lustre and a faint odour of valeric acid. It is not deliquescent, and fuses at a low temperature. Quinine valerate requires 110 parts of cold or 40 of boiling water for solution, and is easily soluble in alcohol. Valerate of quinine is liable to con-

tain much the same impurities as the sulphate (see page 408). Sulphate and hydrochloride of quinine, and valerate and acetate of zinc are also liable to be present.

Quinine Tannate has come into use in medicine on account of its comparatively tasteless character. The commercial product varies greatly in its composition, the bitter taste decreasing with the amount of alkaloid contained in the specimen.

For the preparation of quinine tannate, Peltz recommends the precipitation of a saturated solution of 1 part of quinine hydrochloride by 3 of tannin (in 10 per cent. solution previously neutralised by ammonia). After standing twenty-four hours, the washed precipitate is dried at a low temperature. So prepared, quinine tannate is a yellowish-white amorphous powder, soluble in about 50 parts of cold water or alcohol. Its solution gives the reactions of tannic acid.

In some cases, the quinine in the commercial tannate is largely replaced by other cinchona bases. The following analyses by Jobst (*Arch. Pharm.*, [3], xii. 331; *Jour. Chem. Soc.*, xxxiv. 678) illustrate the composition of commercial "tannate of quinine":—

	1	2	3	4	5	6	7
Water lost at 120° C.	7·2	9·7	9·1	9·8	10·2	10·7	11·4
Quinine, ...	31·37	22·72	4·46	4·93	6·23	10·00	7·40
Quinidine, ...	...	...	11·97	2·43	Trace.	...	...
Cinchonidine, . .	...	...	7·33	13·10	23·80	...	...
Cinchonina, . .	...	...	...	3·35	Trace.	...	...
Total Alkaloid, . .	31·37	22·72	23·76	23·82	27·03	10·00	7·40

To ascertain the proportion of total alkaloid in quinine tannate, Jobst powders 1 gramme of the sample, and mixes it with milk of lime. The mixture is dried on the water-bath, and the resulting powder exhausted with chloroform. The chloroform is filtered, evaporated, and the residue weighed after drying at 120° C. The alkaloid thus separated can be further examined as described on page 412. There seems no reason why the mixture of the sample with milk of lime should not be agitated directly with chloroform, thus avoiding the evaporation to dryness of the aqueous liquid. A similar process is adopted by S. Neumann, who agitates the finely divided tannate with strong solution of caustic alkali and excess of ether. The presence of solid particles

in suspension, either in the ethereal or alkaline solution, shows that the sample is impure or that it has not been completely decomposed.

8. *Quinine Tartrate*, $B_2H_2C_4H_4O_6+H_2O$, forms a crystalline precipitate, soluble in 910 parts of cold and more readily in hot water. It becomes anhydrous at 100°, and is the best form for observing the optical activity of quinine (page 416).

Citrate of Quinine is not a commercial preparation, but in combination with ferric citrate it constitutes the *Ferri et Quininæ Citras, B.P.*

Citrate of Iron and Quinine occurs in commerce in the form of thin transparent deliquescent scales, varying in colour from a delicate greenish golden yellow to yellowish brown, according to the proportion of ammonium citrate present. The preparation should be somewhat slowly, but freely and completely, soluble in cold water. It is insoluble in alcohol or ether. The aqueous solution has a very bitter and chalybeate taste, and should be only very slightly acid. On adding ammonia to the cold solution, white quinine hydrate is thrown down, and the liquid assumes a darker colour. No ferric hydrate is precipitated unless the liquid be heated, or a fixed alkali substituted for the ammonia.

Citrate of iron and quinine is liable to several sophistications.

The proportion of *water* in the sample may be ascertained by drying a weighed quantity in the water-oven. It averages 8 per cent., and should not exceed 10 to 12 per cent.

Adulteration with *potassio-citrate* or *potassio-tartrate* of iron would be detected by the strongly alkaline reaction of the residue left on igniting the substance, a genuine preparation yielding an ash neutral or only very faintly alkaline to litmus paper. The substitution of tartaric acid for the citric acid of the sample is now improbable, but may be detected as described in Volume I.

The proportion of *oxide of iron* can be estimated in the pure preparation with sufficient accuracy by igniting a known weight of the sample. After testing the ash for fixed alkali, a few drops of nitric acid should be added and the residue again ignited. This treatment ensures the complete combustion of the carbon. Citrate of iron and quinine ought to yield from 18 to 20 per cent. of ferric oxide on ignition. A more accurate estimation of the iron can be made in the ash, if desired.

Excess of *citric acid* is indicated by the extra acidity of the sample, but the commercial substance frequently contains a much larger proportion of acid than is prescribed in the *British Pharmacopœia.*

Sulphates are almost invariably present in citrate of iron and

quinine, owing to imperfect washing of the ferric hydrate employed, or to the introduction of the quinine as sulphate instead of precipitated hydrate. The employment of sulphate of quinine is said to render the preparation liable to yield a turbid solution, but it has the advantage of preventing the inevitable loss of alkaloid attending the preparation of quinine hydrate.[1]

The *British Pharmacopœia* of 1867 required that the citrate of iron and quinine should contain 16 per cent. of *alkaloid*, as determined by drying, at an unstated temperature, the unwashed quinine hydrate precipitated by ammonia. In the edition of 1885, this faulty process was substituted by a method recommended by the author (*Analyst*, i. 22), based on the liberation of the quinine from the aqueous solution by ammonia and extraction of the alkaloid by ether or chloroform.[2] No temperature is prescribed for drying the alkaloidal residue, but a constant weight is best obtained at 110°–120°. By this process, which yields very accurate results, the B.P. preparation is now required to yield 15 per cent. of alkaloid.[3] If preferred, the residue may be dissolved in a little alcohol, the solution diluted with water, and titrated with a standard mineral acid and methyl-orange.

The proportion of alkaloid in the citrate of iron and quinine of commerce is often notably less than the 15 per cent. required by the *British Pharmacopœia* (see *Pharm. Jour.*, xvii. 234; xix. 259; xx. 1052). Very commonly only 13 per cent. is present,[4] and

[1] F. W. Fletcher states that a preparation made with sulphate of quinine contains less lime salts than when quinine hydrate is used, since the lime salts introduced in the water employed for washing the alkaline ferric hydrate are retained by the latter, and are subsequently precipitated as calcium sulphate, instead of remaining in the finished product.

[2] To ensure accurate results, the *cold* solution of the sample must be treated with a considerable *excess* of ammonia; the volume of ether or chloroform used should equal that of the ammoniacal liquid, and the agitation should be conducted immediately; the treatment with the solvent should be repeated; and care must be taken that the whole of the precipitated alkaloid is dissolved by the ether. This occurs instantaneously with pure quinine, but if cinchonine has been substituted it will remain undissolved. In such samples, the treatment with ether should be followed by agitation with a mixture of 4 parts of chloroform and 1 of amylic alcohol.

[3] The original issue of the 1885 edition of the *British Pharmacopœia* required 16 per cent. of quinine, as estimated by the ammonia-ether process, but the criticisms of F. W. Fletcher, C. Umney, and others (*Pharm. Jour.*, [3], 263, 406) showed that, if prepared according to the official directions, this proportion was impossible, and the amount was subsequently reduced to 15 per cent.

[4] Chas. Umney (*Pharm. Jour.*, [3], xvii. 285) considers that, the B.P. standard of quality being easily attainable, the manufacture of citrate of iron

occasionally (in the author's experience) from 9 to 11 per cent., even in the case of preparations manufactured by English firms of fairly good repute. Foreign specimens sometimes contain only 4 or 5 per cent. of alkaloid, and that not quinine.

The adulteration of citrate of iron and quinine is not limited to deficiency of total alkaloid, the quinine being sometimes replaced, without acknowledgment, by other cinchona bases. The *British Pharmacopœia* prescribes no test for these, further than requiring the ether-residue to be "almost entirely soluble in a little pure ether." The presence of these bases is best detected by dissolving the alkaloidal residue in sufficient dilute sulphuric acid to convert the bases into neutral sulphates,[1] and treating the resultant solution as described on page 412 *et seq.* To obtain reliable results a considerable quantity of the sample must be employed, but nearly the whole of the quinine is subsequently recovered as crystallised sulphate. By separating this on a calico-filter, pressing it between folds of blotting-paper, and drying it at 100°, the anhydrous sulphate is obtained, and its weight multiplied by 1·18 represents the weight of the crystallised salt. If to this amount there is added 0·00133 gramme for each 1 c.c. of mother-liquor, a very fair direct determination of the quinine sulphate will be obtained; and by multiplying the result by ·735 the corresponding amount of free quinine will be found.

In foreign specimens of citrate, substitution of the quinine by other cinchona bases is common. Amorphous alkaloids are not unfrequently present in considerable proportion.

Tincture of Quinine, B.P., was formerly directed to be made by dissolving 160 grains of crystallised sulphate of quinine in 20 fluid ounces of tincture of orange-peel, by the aid of a gentle heat, the solution being filtered after three days. This was an unsatisfactory preparation, as in cold weather, or when too weak a spirit was used, it was apt to deposit crystals of sulphate of quinine, and so alter in strength. In some cases, at least, the deposit consisted largely of calcium sulphate. In the *Pharmacopœia* of 1885 an equal weight of quinine hydrochloride is substituted for the sulphate, so that the tincture is somewhat stronger than the old preparation. To determine the proportion of quinine in the tincture,

and quinine containing only 13 per cent. of alkaloid, unless it arises from some accident, is a disgrace to pharmacy; and that any pharmacist who sells an article of this character ought to be punished, unless he can show good cause for the deficiency.

[1] This may be effected by adding a moderate excess of hot dilute acid, and then dilute ammonia, drop by drop, until the liquid is neutral to methyl-orange or litmus.

Quinidine (see also page 393) crystallises from alcohol with 2½ aqua in large monoclinic efflorescent prisms or needles. From ether permanent rhombohedra containing 2 aqua are obtained, and from boiling water permanent plates with 1½ aqua. The whole of the water is driven off at 120°. At 160° the anhydrous alkaloid begins to brown slightly, and melts at 168°.

Quinidine resembles quinine in its taste and physiological effects, in being deposited in hydrated crystals from alcohol, in its tolerably ready solubility in ether, in giving the thalleioquin reaction, and in the fluorescence of its solution in dilute sulphuric acid. It is distinguished from quinine by the permanent bulky precipitate its solutions yield on successive treatment with chlorine water, potassium ferricyanide, and ammonia; and also by the very sparing solubility of its *hydriodide.*

Quinidine Sulphate, $B_2H_2SO_4+2H_2O$, crystallises in white needles or long hard prisms which require about 100 parts of cold or 7 of boiling water for solution. It dissolves in 7 parts of cold alcohol, and in 20 of chloroform, but is almost insoluble in ether. The salt differs from the sulphates of the other cinchona alkaloids in requiring a temperature of 120° to render it anhydrous, and in readily taking up the water again in moist air.

Quinidine sulphate is an official remedy in the United States and France. It is examined for other alkaloids by a test slightly modified from one devised by de Vrij (*Pharm. Jour.*, [3], viii. 745), who utilises the fact that quinidine hydriodide requires 1200 parts of water for solution. To test the purity of the commercial sulphate of quinidine, 0·5 gramme is dissolved in 10 c.c. of water at 60° C., and an equal weight of iodide of potassium free from any alkaline reaction added. If the sample be pure, hydriodide of quinidine is precipitated on stirring and cooling as a heavy sandy powder, and if the liquid be allowed to stand for half an hour with frequent agitation and is then filtered, addition of one or two drops of ammonia will cause no turbidity in the clear filtrate. A slight turbidity indicates a trifling admixture of other alkaloids, but if a decided precipitate occur the alkaline liquid should be shaken with a mixture of amylic alcohol and chloroform (see page 431), or chloroform only, and the solvent evaporated to ascertain the proportion and nature of the admixture, which may be cinchonidine or quinine, but is usually cinchonine. The appearance of the precipitated hydriodide is sufficient indication of the presence of impurity, as in the presence of cinchonine or cinchonidine it is resinous instead of being sandy.

For the detection of *inorganic impurities* (*e.g.*, calcium or sodium compounds) in commercial quinidine sulphate, Hesse treats one

gramme of the sample with 7 c.c. of a mixture of 2 volumes of chloroform with 1 of alcohol of 95 per cent. Complete solution will take place in the absence of impurities.

The presence of *cinchonidine* sulphate in the quinidine salt may be detected by treating the sample with pure chloroform. Unless only a very small proportion of the impurity be present, part of it will remain undissolved. Smaller quantities may be detected by shaking the chloroform solution with cold water, in which the whole of the cinchonidine and part only of the quinidine salt will dissolve, and the former will be precipitated on addition of Rochelle salt.

A solution of quinidine sulphate in chloroform is at first colourless, but on keeping becomes yellow with a slight green reflection.

Quinamine. $C_{19}H_{24}N_2O_2$.

This alkaloid was first discovered by Hesse in the bark of *Cinchona succirubra*, and has since been detected in *C. officinalis*, *rosulenta*, and several varieties of *Cinchona Calisaya*, particularly *Ledgeriana*.[1]

Quinamine crystallises in delicate hair-like anhydrous needles, which melt at 172° C. Its rotatory power in alcoholic solution is $+104{\cdot}5°$ for the sodium ray.

Quinamine is nearly insoluble in cold water, more readily in boiling. Hot alcohol dissolves it freely. It also dissolves in boiling ether, petroleum spirit, and benzene.

Quinamine itself is almost tasteless, but its solutions in acids are very bitter. The solution in excess of dilute sulphuric acid exhibits no fluorescence. Acid solutions of quinamine are very prone to decomposition with formation of an amorphous alkaloid called quinamidine, isomeric with quinamine. Quinamicine is also formed as a bye-product, and under certain conditions apoquinamine, $C_{19}H_{22}N_2O$, results. When tested with chlorine or bromine water and ammonia, solutions of quinamine yield a yellowish amorphous precipitate, but no green colour. The solid alkaloid, when moistened with strong nitric acid, gives a yellow coloration.

CONQUINAMINE, $C_{19}H_{24}N_2O_2$, occurs with quinamine, but in

[1] The mother-liquors from the crystals of quinine sulphate are precipitated with Rochelle salt, the filtrate treated with ammonia, and the precipitate washed with ether. The ethereal washings are treated with acetic acid, the liquid neutralised, and while warm treated with potassium thiocyanate, till on cooling cinchonine can no longer be detected. Quinidine is then precipitated, together with colouring matter. The filtered liquid is treated with soda, and the resinous precipitate dissolved in a minimum of hot 80 per cent. alcohol, from which quinamine crystallises on cooling.

smaller proportion. It may be separated from the latter base by fractional crystallisation of the nitrates, oxalates, or hybromides, the conquinamine salts being in each case the less soluble (*Annalen*, ccix. 38, 62). Conquinamine forms colourless or golden-yellow tetragonal crystals, melting at 121°–123°, easily soluble in ether, chloroform, and benzene. $S_D = +204{\cdot}1°$ for a 4 per cent. in alcohol. $B_2H_2SO_4 + x$ aqua is *very soluble*. The *aurochloride* is a yellow precipitate, becoming purple. Conquinamine closely resembles quinamine. When heated with concentrated hydrochloric acid, it yields apoquinamine, $C_{19}H_{22}N_2O$.

Cinchonidine. $C_{19}H_{22}N_2O$.[1] (See also page 392.)

This base is contained in several species of cinchona, but is especially characteristic of the red bark of *C. succirubra*. According to D. Hooper the *absence* of cinchonidine is a distinctive character of Remijia barks. It was formerly called quinidine.

Cinchonidine crystallises in short anhydrous prisms or thin plates, soluble in 16 parts of alcohol and 188 of ether. It is readily soluble in amylic alcohol and chloroform. It is lævo-rotatory, S_D (where $c = 4$ and $t = 15°$ C.), in chloroformic solution being $-70{\cdot}0°$; while in dilute hydrochloric acid solution ($c = 5$) $S_D = -174{\cdot}6°$.

Cinchonidine resembles quinine in the direction of its optical activity, in the insolubility of the anhydrous neutral sulphate in chloroform, and in the sparing solubility of the tartrate in water. According to Hesse, it forms a crystalline compound with quinine containing $C_{20}H_{24}N_2O_2 + 2C_{19}H_{22}N_2O$. It is distinguished from quinine by its lesser specific rotation, its more sparing solubility in ether, its non-fluorescence, by not giving the thalleioquin reaction, and by the greater solubility of its neutral and acid sulphate and iodosulphate. The accurate separation of cinchonidine from quinine presents great difficulties, and is discussed at length on page 411 *et seq.* Cinchonidine has only about one-fourth of the therapeutic activity of quinine.

Cinchonidine is isomeric with cinchonine, from which it differs by its lævo-rotation; its greater solubility in ether; the insolubility of its tartrate in water; the insolubility of the anhydrous sulphate in chloroform; and the formula of the crystallised sulphate.

The normal *salts of cinchonidine* are neutral to litmus and methyl-orange, but acid to phenolphthaleïn. Thus the precipitated tartrate

[1] Cinchonidine was formerly believed to contain $C_{20}H_{24}N_2O$; but its conversion by heating with concentrated hydrochloric acid into apocinchonidine, $C_{19}H_{22}N_2O$, without formation of methyl chloride, and analyses of hydrochloride, sulphate, and chloroplatinate establish the formula given in the text.

reacts to the last indicator like an equivalent amount of free tartaric acid, and the combined alkaloid can be estimated by titration in presence of alcohol with standard caustic soda or baryta. Adhering Rochelle salt does not interfere.

The following table shows the formulæ and solubilities of the principal salts of cinchonidine :—

Salt.	Formula.	Appearance.	Solubility in Water.	
			Cold.	Hot.
Hydrochloride, .	$BHCl+1$ aq.	Double pyramids or octahedra.	30	Readily soluble.
Hydrobromide, .	$BHBr+1$ aq.	Long colourless needles.	40	Freely soluble.
Sulphate, . . .	$B_2H_2SO_4+x$ aq.	Silky lustrous needles, or thin quadratic prisms.	100	4
Oxalate, . . .	$B_2H_2C_2O_4+6$ aq.	Prismatic crystalline powder.	252 at 12°	...
Tartrate, . . .	$B_2C_4H_6O_6+2$ aq.	Crystalline precipitate.	1265 at 10°	...

Cinchonidine sulphate, $B_2H_2SO_4$, is remarkable for the number of hydrates it is capable of forming. From a moderately concentrated aqueous solution it crystallises with 6 aqua in brilliant needles; from a hot and concentrated aqueous solution in hard prisms or acicular silky crystals containing 3 aqua (official in the *B.* and *U.S. Pharmacopœias*); and from alcohol in fine prisms with 2 aqua. A hydrate containing 5 aqua has been described by Hesse.[1] The 6-atom hydrate is somewhat efflorescent. All water is lost at 100°, and 2 aqua re-absorbed in moist air.

Cinchonidine sulphate is sometimes contaminated with an admixture of the corresponding salts of cinchonine and quinidine. To detect these, Hesse (*Zeitsch. Anal. Chem.*, xv. 464) dissolves 0·5 gramme of the salt in 20 c.c. of water at 60° C., and adds 1·5 gramme of Rochelle salt. A crystalline precipitate of the sparingly soluble cinchonidine tartrate is produced. After standing one hour the liquid is filtered, and the filtrate tested with a drop of ammonia. Any turbidity or precipitate is due to the presence of more than 0·5 per cent. of cinchonine or 1·5 per cent. of quinidine. These may be distinguished by treating the filtrate with potassium iodide as described on pages 413 and 426.

Hager recommends the use of 0·1 gramme of cinchonidine

[1] Five commercial samples of cinchonidine sulphate examined by A. B. Prescott, lost, at 100° C., proportions of water ranging from 6·86 to 7·04 per cent. $B_2H_2SO_4+3$ aqua requires 7·30 per cent.

sulphate, 0·3 of Rochelle salt, and 20 c.c. of cold water. The liquid is frequently agitated, filtered after one hour, and tested with a few drops of ammonia. As thus performed, the test is less strict than that of Hesse, but perhaps, on that account, is better suited for medicinal purposes.

The precipitate of cinchonidine tartrate obtained in the above tests is soluble in about 1200 parts of cold water, but almost wholly insoluble in a strong solution of Rochelle salt. After drying at 100° C., it contains 80·84 per cent. of cinchonidine. It will contain quinine if any of that base were present in the sample. In such case the solution of the precipitate in excess of dilute sulphuric acid will be notably fluorescent.

Hesse has also proposed to distinguish the sulphates of the cinchona bases by their behaviour with chloroform. The *anhydrous* neutral sulphates of quinine and cinchonidine are almost insoluble in alcohol-free chloroform, while the corresponding salts of cinchonine and quinidine dissolve readily (see pages 416, 427). Cinchonidine sulphate requires, when anhydrous, 300 of boiling or 1000 parts of cold chloroform, the undissolved portion becoming gelatinous. In the presence of cinchonine or quinidine sulphate its solubility in chloroform is increased. According to the *British Pharmacopœia* (1885), cinchonidine sulphate (crystallised) is soluble in ether, a statement which is misleading, and correct only to a very limited degree. The *U.S. Pharmacopœia* describes it "very sparingly soluble in ether or benzene."

The presence of quinidine and quinine in cinchonidine sulphate can be recognised by the thalleioquin reaction and the fluorescence of the solution in dilute sulphuric acid.

HOMOCINCHONIDINE, $C_{19}H_{22}N_2O$ (see also page 392), accompanies cinchonidine in many cinchona barks, especially that of *C. rosulenta*, and passes into the dark sulphate mother-liquors in the quinine manufacture. It crystallises from alcohol in anhydrous prisms, or from a dilute solution in leaflets, almost insoluble in water, but soluble in chloroform. $B_2H_2SO_4 + 6H_2O$ crystallises from hot water in white needles, but from strong solutions the salt separates as a white mass, which after drying resembles magnesia.

Hesse states that homocinchonidine is an essentially different substance from cinchonidine, and that it is not possible to convert one into the other. The two bases may be separated by fractional crystallisation of their sulphates from aqueous solution. In presence of quinine sulphate, the homocinchonidine salt is said to crystallise in the form of cinchonidine sulphate.

HYDROCINCHONIDINE, $C_{19}H_{24}N_2O$, possibly identical with cinchonidine, occurs in the mother-liquors from homocinchonidine.

Cinchonine. $C_{19}H_{22}N_2O$; or $C_9H_7N.C_9H_{11}(OH)N.CH_3$.[1]
This important alkaloid is almost invariably present in cinchona barks. When the free bases are crystallised from alcohol the cinchonine is deposited before the quinine; unless the latter base is present in relatively large amount, in which case the greater part should be previously removed by crystallising the sulphates.

Cinchonine crystallises from alcohol in anhydrous shining prisms or needles. It melts at 165° C. to a colourless liquid, and partially sublimes at a higher temperature. According to Hlasiwetz, it may be readily sublimed in a current of hydrogen or ammonia.

Cinchonine is almost insoluble in cold water, and requires 2500 parts of boiling water for solution.

One part of cinchonine dissolves in 120 parts by weight of cold rectified spirit or 28 of boiling alcohol, in 350 parts of chloroform, in 371 of ether, and in 109 parts of amylic alcohol. It requires only about 13 parts of a mixture of 6 grammes of chloroform with 1 of rectified spirit, and is soluble in 23 parts of a mixture of 4 of chloroform and 1 of amylic alcohol.

A. B. Prescott found the following to be the solubility of cinchonine in different physical conditions, and at the boiling-point of the solvent:—

Condition of Alkaloid.	Parts by Weight of Washed Solvent required.			
	Ether.	Chloroform.	Amylic Alcohol.	Benzene.
Crystallised, . .	719	828	...	...
Amorphous, . .	563	...	...	...
"Nascent,"[2] . .	526	178	22	876

It will be seen from these results that amylic alcohol is by far the best solvent for cinchonine, except a mixture of amylic alcohol and chloroform. On the other hand, ether is the best solvent for effecting an approximate separation of cinchonine from quinine.

When heated to a high temperature with an alkali, cinchonine yields quinoline, C_9H_7N (page 115), together with other products. With iodine trichloride, cinchonine yields a yellow precipitate.

[1] The constitution of cinchonine is discussed on page 168.

[2] To obtain the alkaloid in the "nascent" state, the solvent was added to its sulphuric acid solution, which was then warmed to the boiling-point of the former. The liquid was next made slightly alkaline with ammonia, shaken, kept warm for five minutes, and filtered.

Cinchonine is not precipitated in the cold from a solution containing tartaric acid by adding sodium hydrogen carbonate. On heating the liquid, however, carbonic acid escapes and cinchonine is separated.

The precipitate formed by ammonia in solutions of cinchonine is not soluble in excess of the reagent. The precipitate is amorphous when first produced, but speedily becomes crystalline.

Cinchonine is sharply distinguished from quinine by the very limited solubility of the free base in ether, by the solubility of the anhydrous neutral sulphate in chloroform, by its failure to give the thalleioquin reaction, by its dextro-rotatory power, and by the non-fluorescence of its solution in excess of dilute sulphuric acid. Methods of detection and separation based on these facts are given on pages 413 and 416.

Cinchonine Sulphate, $(C_{19}H_{22}N_2O)_2H_2SO_4 + 2H_2O$, forms short, hard, shining, clino-rhombic prisms, with dihedral summits. The salt becomes anhydrous at 100° C., and melts with partial decomposition at about 240° C. Cinchonine sulphate has a very bitter taste, dissolves in 54 parts of cold water, and is readily soluble (1 : 6) in alcohol. It is insoluble in ether or benzene. The *anhydrous* salt is soluble in 60 parts of cold or 22 of boiling chloroform, a fact which distinguishes it from the sulphates of cinchonidine and quinine.

A solution of cinchonine sulphate does not give the thalleioquin reaction, and is not rendered fluorescent by dilution with very weak sulphuric acid.

The mode of assaying of cinchonine sulphate is sufficiently indicated under the head of "Quinine Sulphate" (page 408 *et seq.*).

Cinchonine Hydrochloride, $C_{19}H_{22}N_2O,HCl + 2H_2O$, is readily soluble in water and alcohol, and somewhat so in ether and chloroform. It has been not unfrequently employed to adulterate sulphate of quinine. In such case the solution of the sample in very dilute sulphuric or nitric acid will give a white, curdy precipitate of silver chloride on adding silver nitrate. Cinchonine will be detected by the tests for that alkaloid.

When heated in a dry test-tube, cinchonine hydrochloride gives purple fumes much resembling the vapour of iodine. The *sulphates* of the cinchona bases do not give this reaction.

HYDROCINCHONINE, $C_{19}H_{24}N_2O$, is stated by Hesse to occur in cuprea bark.

CINCHOTINE, $C_{19}H_{24}N_2O$ (see page 392) is isomeric with cinchonamine (page 438). It dissolves very sparingly in ether (1 : 500). $BHCl + 2$ aqua requires about 48, and $B_2H_2SO_4 + 12$ aqua about 35 parts of cold water for solution.

CINCHAMIDINE is a base probably isomeric with the above, and identical with hydrocinchonidine (page 430).

Amorphous Cinchona Bases.

Certain uncrystallisable alkaloids exist ready-formed in cinchona barks, the proportion present being probably affected by sunlight and the presence of any free acid in the bark.

In the preparation of the salts of the alkaloids from cinchona bark, a further portion of the bases undergoes conversion into a resinoid substance known in commerce as "quinoïdine" or "amorphous quinine."

QUINOÏDINE is obtained in quinine factories by precipitating the brown mother-liquors with ammonia, and consists largely of two alkaloids, quinicine and cinchonicine, which are isomeric with and appear to be due to the action of heat on quinine or quinidine, and cinchonine or cinchonidine, respectively. These amorphous products may also be obtained by heating the crystallised bases in glycerin to a temperature of 200° C., a red substance being formed at the same time.

Commercial quinoïdine is a dark brown, brittle, "extractiform" mass, softening below 100° C., and having usually a slight alkaline reaction. It is a product of indefinite composition which has never been very favourably regarded in this country, though it has received official recognition in the *German* and *United States Pharmacopœias.* Both works limit the ash to 0·7 per cent. By the latter it is described as almost insoluble in water, freely soluble in alcohol, chloroform, and dilute acids, and partly soluble in ether and benzene. When triturated with boiling water, the liquid, after filtration, should be clear and colourless, and should remain so after addition of an alkali. The *German Pharmacopœia* requires that quinoidine should dissolve clear in an equal weight of 1 part of dilute acetic acid with 9 parts of water, so as to leave scarcely any residue; and it must also form a clear solution with nine times its weight of cold dilute spirit. Quinoidine is said to be liable to adulteration with mineral matters, resins, liquorice, glucose, &c., all of which sophistications would be detected by one or other of the above tests.

For the purification of quinoïdine it is recommended to digest the commercial article on the water-bath, with 2 parts of benzene, while stirring or agitating. The clear solution is poured off, and the residue washed with more benzene. The benzene solution is then shaken with a slight excess of dilute hydrochloric acid, the acid liquid separated, and rendered faintly alkaline by caustic soda. A portion of this solution is then tested for purity

by dilution and addition of a few drops of a concentrated solution of sodium thiosulphate (hyposulphite), which ought not to produce any precipitate insoluble on a further addition of water. Should impurity be indicated, the whole of the solution of quinoïdine hydrochloride must be treated with sodium thiosulphate as long as a permanent precipitate is produced. The liquid is then filtered, warmed, treated with excess of soda, and the precipitated quinoïdine washed with water and dried at 100°.

Thus purified, quinoïdine appears in thin layers as a dark yellowish brown, transparent mass. It is completely soluble in benzene, alcohol and acids, and ether should dissolve at least 70 per cent. of it. The normal salts of quinoïdine are said to have an alkaline reaction, and should be soluble in water in all proportions. When impure they form a clear solution in a little water, but the liquid becomes turbid on further dilution.

To prepare a pure amorphous alkaloid, the acid sulphate of quinine or cinchonidine, according to the product required, is first rendered anhydrous by careful drying at 100° C., and is then raised for a few minutes to a temperature of 130° to 135° C., when it melts and is wholly converted into the acid sulphate of the new alkaloid.

Quinicine, $C_{20}H_{24}N_2O_2$, is a yellowish, amorphous, anhydrous body, which melts at about 60° C., assuming a reddish-brown colour which becomes darker at 100°. It is nearly insoluble in water, but has a bitter taste. The alcoholic solution has a strong alkaline reaction, and absorbs carbon dioxide from the air. The alkaloid is readily soluble in chloroform or ether. Quinicine gives a green coloration when treated in solution with chlorine- or bromine-water and ammonia, but is distinguished from quinine and quinidine by producing a white amorphous precipitate with sodium hypochlorite or solution of bleaching powder. In applying this test the liquid should be slightly, but not strongly, acidulated with hydrochloric acid. Quinicine may be separated from the accompanying alkaloids by adding ammonia, when the ammonium salt formed dissolves the liberated alkaloid, which may then be recovered by agitation with ether. If soda be employed instead of ammonia the alkaloid is thrown down as an oily mass.

A solution of quinicine in excess of dilute sulphuric acid has a yellow colour but exhibits no fluorescence.

Quinicine forms crystallisable compounds with acids, and double salts with the chlorides of platinum and gold. Neutral oxalate of quinicine dissolves readily in hot chloroform, alcohol, or water. In solution in a mixture of alcohol and chloroform the oxalate exhibits a right-handed rotation corresponding to a value of $S_D = +25{\cdot}8°$ for the alkaloid.

Quinicine solutions are not precipitated by Rochelle salt. They are completely precipitated by adding excess of potassium thiocyanate, which throws down quinicine thiocyanate as an oil which subsequently solidifies. It is soluble in pure water, but insoluble in solutions of alkaline thiocyanates.

Cinchonicine, $C_{19}H_{22}N_2O$, when precipitated by soda from the solution of one of its salts, forms a yellow viscous mass readily drawn out into colourless strings. It liquefies at about 50° C., and at 80° turns brown. At higher temperatures (*e.g.*, 100° C.) it becomes dark brown, and is converted into a substance resembling "quinoïdine." Upon cooling it remains soft. As deduced from the rotatory power of the oxalate, in alcoholic, aqueous, or chloroformic solution, the value of S_D for cinchonicine is +20·1°.

In most reactions, including its behaviour with ammoniacal salts and with hypochlorites, cinchonicine closely resembles quinicine, and hence is distinguished from cinchonine and cinchonidine. It is distinguished from quinicine by giving no green colour with chlorine- or bromine-water and ammonia.

Cinchonicine is bitter, and in the free state has a strongly alkaline reaction. It neutralises acids perfectly, and many of the resultant salts are crystallisable.

Anhydro-Bases. Certain amorphous bases, distinct from quinicine and cinchonicine, exist ready-formed in cinchona barks. They are not convertible in quinicine or cinchonicine, and appear to be formed by the coalescence of two molecules of the crystallisable alkaloids, accompanied in the case of quinine and quinidine with the elimination of a molecule of water. Thus:—

$$\underset{\text{Quinine or Quinidine.}}{2C_{20}H_{24}N_2O_2 - H_2O} = \underset{\text{Diquinicine.}}{C_{40}H_{46}N_4O_3}.$$

$$\underset{\text{Cinchonidine or Cinchonine.}}{2C_{19}H_{22}N\,O} = \underset{\text{Dicinchonicine.}}{C_{38}H_{44}N_4O_2}.$$

These bases constitute the greater part of the amorphous alkaloid contained in commercial quinoïdine. They are wholly amorphous, as also are all their salts. The solution of diquinicine in excess of dilute sulphuric acid is fluorescent, gives the thalleioquin reaction, and is dextro-rotatory. Dicinchonicine does not possess these characters.

De Vrij has pointed out a distinction between quinicine, cinchonicine, and the natural amorphous alkaloids. If the neutral oxalates of the bases be rendered anhydrous by heating at 100° C., and the dry salts treated with chloroform, they behave in a characteristic manner. Oxalate of *quinicine* dissolves sparingly

in chloroform at the ordinary temperature, but freely in the boiling liquid. On cooling, the solution deposits the greater part of the oxalate in crystals. Anhydrous oxalate of *cinchonicine* dissolves freely in cold chloroform. By adding a few drops of water on the surface, the solution is transformed in a few minutes into a solid mass. The oxalates of the *natural amorphous alkaloids* are very soluble in chloroform. The solution remains clear on adding a few drops of water, but the water dissolves out some of the oxalate from its chloroformic solution. The amorphous oxalate is highly deliquescent, but the oxalates of quinicine and cinchonicine remain unchanged in the air.

Alkaloids of Remijia Barks.

The barks of the various species of *Remijia* vary greatly in the alkaloids which they contain. Thus, while the bark of *R. pedunculata* contains quinine and the allied alkaloid cupreine, that of *R. Purdicana*, which anatomically closely resembles the former, and has been confounded with it, contains no alkaloid closely related to quinine except comparatively small proportions (0·1 to 0·2 per cent.) of cinchonine and cinchonamine. Cusconidine, which occurs in the bark of *R. Purdieana*, is also found in that of *Cinchona Pelletierana*, together with cusconine and aricine, which two bases do not appear to be present in Remijia bark. The bases isolated from this bark by Hesse were (in addition to cinchonine and cinchonamine) concusconine, chairamine, conchairamine, chairamidine and conchairamidine, the formulæ and certain characters of which are given on page 393.[1]

[1] To extract the whole of the alkaloids, amounting to 2 to 3 per cent., Hesse treated the finely-ground bark with hot alcohol, distilled off the solvent, treated the residue with excess of soda, and agitated with ether. On shaking the separated ethereal layer with dilute sulphuric acid, a pale yellow, curdy mass (A) separated, a portion of which remained suspended in the ether and part in the yellow acid liquid (B). On separating the latter (B) and adding very dilute nitric acid, *cinchonamine* nitrate was precipitated (mixed with the nitrates of some of the bases of group A), while *cinchonine* remained in solution. The curdy precipitate (A) was digested with dilute soda, the liberated alkaloids washed and air-dried, dissolved in hot alcohol, and treated with one-eighth of their weight of sulphuric acid (H_2SO_4). Almost all the *concusconine* immediately precipitated as sulphate, a small additional quantity separating on cooling. Hydrochloride of *chairamine* was precipitated on adding strong hydrochloric acid to the cold alcoholic mother-liquor. The filtrate from this was warmed and treated with a little potassium thiocyanate, and the precipitate of *conchairamine* thiocyanate filtered off. On adding more of the reagent, till the dark coloured solution became light brown, a pitchy mass separated, after the removal of which the solution was treated with excess of ammonia and shaken

Concuscamidine does not appear to be a definite substance. All these alkaloids, like aricine and cusconine, contain four atoms of oxygen, and form a group only distantly related to cinchonine and cinchonamine. Concusconine has the same empirical formula as cusconine, aricine, and brucine, and resembles the strychnos alkaloids in some of its reactions. It crystallises with 1 aqua, and is dextro-rotatory, while cusconine has a lower melting-point, crystallises with 4 aqua, and rotates to the left. Concusconine resembles chairamine and its isomers in giving a deep green coloration when the solution in hydrochloric or sulphuric acid is mixed with concentrated nitric acid, a reaction which is not common to cusconine or aricine. *Echitamine* or *ditaïne*, an alkaloid contained in the bark of *Alstonia scholaris*,[1] only differs by H_2 from chairamine and its isomers, to which it presents a considerable resemblance. *Alstonine*, $C_{21}H_{20}N_2O_4$, an amorphous alkaloid, which occurs together with *alstonidine* and *porphyrine* in the bark of *Alstonia constricta*, is strongly fluorescent in acid solutions, and is not improbably related to the cusconidine group. Hesse suggests that *gelsemine*, $C_{24}H_{28}N_2O_4$, the poisonous alkaloid from the root of *Gelsemium sempervirens* (yellow jesamine), is related to these alkaloids, and points out that the coloration it gives with nitric acid somewhat resembles the reaction of concusconine.

with benzene. The benzene was extracted with acetic acid, and the acetic solution treated with a saturated solution of ammonium sulphate, which precipitated a mixture of the sulphates of *chairamidine* and *conchairamidine*, separable by fractional crystallisation from hot water, in which the latter salt is the less soluble.

[1] Dita Bark, from *Alstonia* or *Echites scholaris* (Philippine Islands), has febrifuge properties, and contains the following alkaloids, together with several peculiar indifferent bodies. For the extraction and separation of the alkaloids the bark is extracted with hot alcohol, the solvent distilled off, the residue treated with ammonia and shaken with ether, which dissolves the *ditamine*. The residue is treated with solid caustic potash and extracted with chloroform, which is evaporated, and the residue treated with concentrated hydrochloric acid,' when *ditaïne* hydrochloride separates while echitenine remains dissolved.

DITAÏNE, or ECHITAMINE, $C_{22}H_{28}N_2O_4 + 4$ aqua, forms glassy prisms. Melts at 206°. $S_D = -28{\cdot}8°$. Very bitter. Moderately soluble in water, alcohol, and ether. A strong base, not precipitated by ammonia. Decomposes sodium chloride, setting free caustic soda. Reduces Fehling's solution after boiling with hydrochloric acid. Concentrated sulphuric acid dissolves ditaïne with purple-red colour; nitric acid gives a purple-red, changing to green.

DITAMINE, $C_{19}H_{19}NO_2$, an amorphous powder melting at 75°, soluble in alcohol, ether, and chloroform.

ECHITENINE, $C_{20}H_{27}NO_4$; brownish, amorphous, melting above 120°. Forms amorphous salts.

A full description of the alkaloids of *Remijia Purdieana* and *Cinchona Pelletierana* barks has been published by O. Hesse (*Annalen*, clxxxv. 296, 323; ccxxv. 211; *Jour. Chem. Soc.*, xxxviii. 155; xlviii. 64; *Pharm. Jour.*, [3], xv. 772). Aricine has been recently re-investigated by Moissan and Langrin (*Compt. Rend.*, cx. 469). Cinchonamine and cupreine are described below.

CINCHONAMINE, $C_{19}H_{24}N_2O$ (see page 393), occurs in the bark of *Remijia Purdieana* (false cuprea bark), a tree growing in the Columbian provinces of Antioquia. Its isolation is described on page 436. It is soluble in alcohol, ether, chloroform, benzene, and carbon disulphide, but only sparingly in water or petroleum spirit. It is very bitter, poisonous,[1] yields no methyl chloride when heated with strong hydrochloric acid, gives no reaction with ferric chloride, and no colour with the thalleioquin test. It is said to be insoluble in strong hydrochloric acid, but dissolves in strong nitric acid with bright yellow, and in strong sulphuric acid with reddish-yellow colour. $B_2H_2SO_4$ forms colourless prisms, *readily soluble in cold water*. $BHNO_3$ forms short prisms melting at 195°, and very sparingly soluble in cold water (1 : 500).

CUPREINE, $C_{19}H_{22}N_2O_2$, or $C_{19}H_{20}(OH)N_2.OH$. This interesting alkaloid was discovered by Paul and Cownley in the bark of *Cinchona cuprea* or *Remijia pedunculata*, a tree growing in the districts surrounding the Magdalena River and the Upper Orinoco. Since 1881, cuprea bark has been largely used for the manufacture of quinine.[2]

Cupreine crystallises from alcohol in the anhydrous form, but from ether in concentric prisms containing 2 aqua. When the alcoholic solution is diluted with water, the precipitate contains $B_3 +$ aqua. The hydrates lose their water at 125°. Cupreine is only sparingly soluble in ether or chloroform, but readily in alcohol. The alcoholic solution is lævo-rotatory ($S_D = -175{\cdot}3°$), alkaline, gives a dark reddish brown coloration with ferric chloride, and responds to the thalleioquin test. The solution of cupreine in dilute sulphuric acid is not fluorescent. The free base precipitated by

[1] Sée and Bockefontaine (*Compt. Rend.*, c. 366) found cinchonamine (sulphate) six times as toxic as quinine, cinchonidine, or cinchonine. An injection of 0·25 gramme killed a guinea-pig in a few minutes.

[2] For the preparation of cupreine, the crude quinine sulphate from the cuprea bark is dissolved in dilute sulphuric acid, excess of caustic soda added, and the quinine extracted by agitation with ether. The separated alkaline liquid is neutralised with sulphuric acid, when cupreine sulphate crystallises out. The sulphate is treated with ammonia and boiling ether, from which the cupreine crystallises on cooling.

ammonia is only slightly soluble in excess, and may be extracted by ether. When cupreine is liberated from a salt by a fixed caustic alkali, it dissolves on adding an excess of the reagent, forming (with soda) a definite crystallisable compound containing $C_{19}H_{21}N_2O.ONa$, from the solution of which the alkaloid cannot be extracted by ether.[1] This behaviour is due to the presence of a hydroxyl-group having a phenolic character (compare Morphine, page 311). The cupreinates of potassium and sodium are very soluble in water, and the corresponding compounds of calcium, lead, and silver have a strong alkaline reaction, and are more or less soluble in water. From the fact that alkalies form only mono-derivatives, while two atoms of the hydroxyl of cupreine can be replaced by acetyl,[2] it is probable that the hydroxyl-atoms have different functions, as is the case with those of the morphine-molecule.

When heated with hydrochloric acid (sp. gr. 1·125) to 140°, cupreine is converted into apoquinine, without formation of methyl chloride.

The conversion of cupreine into quinine is described on page 398.

Cupreine yields two classes of *salts*. Those of the general formula $B\bar{A}$ are sparingly soluble, and the aqueous solutions have a yellow colour, though their alcoholic solutions are perfectly colourless. The salts of the formula $B\bar{A}_2$ are, as a rule, pretty freely soluble, and their aqueous solutions are colourless.

Cupreine Sulphate, $B_2H_2SO_4+6H_2O$, crystallises in minute white needles, very difficultly soluble in cold water, and insoluble in a saturated solution of sodium sulphate. $BH_2SO_4+H_2O$, crystallises in prisms sparingly soluble in cold water. *Cupreine tartrate* forms delicate efflorescent needles, very sparingly soluble in cold water. *Cupreine thiocyanate* is produced on adding potassium thiocyanate to a hot solution of the monohydrochloride. The liquid becomes turbid and gradually deposits acicular crystals of the salt. It is very sparingly soluble in, and is precipitated in an oily form by, an excess of the precipitant.

HOMOQUININE. When molecular proportions of quinine and

[1] When cupreine and caustic potash or soda are mixed in molecular proportions, a portion of the alkaloid (10 to 20 per cent.) is extracted on agitation with ether, but this may be prevented by using some excess of alkali.

[2] DIACETYL-CUPREINE, $C_{19}H_{20}(C_2H_3O)_2N_2O_2$, was obtained by Hesse by heating cupreine with acetic anhydride to 85° for a few hours. It forms hexagonal plates melting at 88°, and is soluble in alcohol, chloroform, and ether. The alcoholic solution is strongly alkaline, gives no colour with ferric chloride, but is turned dark green by chlorine and ammonia. By caustic alkalies, the base is hydrolysed in a few minutes with formation of cupreine and acetic acid

cupreine are dissolved in dilute acid, and the solution precipitated by ammonia and shaken with ether, the solvent deposits on evaporation characteristic crystals[1] of a molecular compound of quinine and cupreine containing $C_{20}H_{24}N_2O_2, C_{19}H_{22}N_2O_2 + 4$ aqua. The same substance is readily obtainable by precipitating a solution of sodium cupreinate with one of quinine hydrochloride :—

$$C_{20}H_{24}N_2O_2,HCl + C_{19}H_{21}N_2O.ONa = NaCl + C_{20}H_{24}N_2O_2, C_{19}H_{21}N_2O.OH.$$

This remarkable compound was discovered and described simultaneously by Howard and Hodgkin (*Jour. Chem. Soc.*, xli. 66), Paul and Cownley (*Pharm. Jour.*, [3], xii. 497), and W. G. Whiffen under the name of homoquinine, prior to the isolation of cupreine by Paul and Cownley (*Pharm. Jour.*, [3], xv. 221). It forms salts, having different characters from those either of quinine or cupreine, and is only resolved into its constituents by precipitating the solution with excess of caustic soda, when the quinine may be shaken out with ether, while the cupreine remains in the alkaline liquid as sodium cupreinate.

The analytical differences between homoquinine and cupreine have been fully described by Paul and Cownley (*Pharm. Jour.*, [3], xv. 402).

Cinchona Barks.[2]

The bark of various species of *Cinchona*, which, with about thirty other allied genera, constitute the tribe *Cinchoneæ* (order, *Rubiaceæ*), have been long known for their antifebrile properties. These properties are chiefly due to peculiar alkaloids contained therein, which alkaloids are absent from all the allied genera, except certain species of *Remijia.*

Nearly forty species of cinchona have been described, many of which can only be discriminated with great difficulty. The cinchonas form a very intricate genus, one series running into another through a series of intermediate forms, the number of which is limited to some extent in their native country by the fact that particular species are practically confined to certain districts and elevations.

Only some seven distinct species of cinchona yield bark of any practical importance. These are :—

a. Pale or *Crown Bark*, yielded by *Cinchona officinalis* (Peru) and allied species. It occurs in quills, with a rough, blackish-brown or dark grey surface. (For analyses, see page 446 *et seq.*)

[1] Homoquinine is deposited from ether in very thin prismatic laminæ, having characteristically-shaped ends terminated with two oblique planes.

[2] French ; *Ecorces de Quinquina.* German ; *Chinarinden.*

b. Yellow or *Calisaya Bark* is, with the exception of Ledger bark, the richest of all the cinchona barks. It now usually occurs in quills having a rough surface, but formerly was met with in flattened pieces known as "flat yellow bark."

c. Red Bark, from *C. rubra* and *C. succirubra*, is distinguished by the red colour of the sap and mature bark. It is extensively cultivated in India, and is remarkable for the large proportion of cinchonidine contained in it. (For analyses, see page 446 *et seq.*

d. Pitayo Bark, from *C. Pitayensis*, is imported in short, brownish, curly pieces, rich in quinine and quinidine.

e. Columbian and *Carthagena Barks*, from *C. lucumifolia* and *lancifolia*, are imported in soft quills or broken pieces of very variable quality. Quinine is often wholly absent (*Year-Book Pharm.*, 1888, page 425).

f. Ledger Bark, from *Cinchona Ledgeriana*, is the richest in quinine of all cinchona barks.

g. Cuprea Bark, yielded by *Remijia pedunculata*, is not a true cinchona bark, and is the only known species of any other genus which yields quinine, though the allied alkaloid cinchonamine (page 438) has been found in *R. Purdieana*. Cuprea bark is peculiar in containing the interesting alkaloid cupreine[1] (page 438).

Hybrid barks are often produced, especially crosses between *C. officinalis* and *C. succirubra* (see page 447).

A concise description of the chief kinds of cinchona bark, with their distinguishing characteristics, has been published by W. Elborne (*Pharm. Jour.*, [3], xiv. 653).

The *British Pharmacopœia* of 1885 gives the following as the characters of official (red) cinchona bark, from *Cinchona succirubra*:—

"In quills, or more or less incurved pieces coated with the periderm, and varying in length from usually a few inches to a foot or more—the bark itself from about one-tenth to a quarter of an inch thick, or rarely more; outer surface more or less rough from longitudinal furrows and ridges, or transverse cracks, annular fissures, and warts, and brownish or reddish-brown in colour; inner surface brick-red or deep reddish-brown, irregularly and coarsely striated; fracture nearly close in the smaller quills, but finely

[1] Formerly, the cinchona trees were invariably cut down and the bark stripped off and dried in the sun or on hurdles over a fire. A greatly improved plan is to make longitudinal incisions in the bark of the growing tree, remove about half the bark, leaving the remainder intact, and cover the stem with moss. Fresh bark is then formed very rapidly, and this renewed bark not only contains a larger percentage of total alkaloids than the original, but the alkaloids contain a very much larger proportion of quinine.

fibrous in the larger ones; powder brownish or reddish-brown; no marked odour; taste bitter and somewhat astringent."[1]

The characters which conventionally determine the market-value of "druggists' quills" are often very fallacious, and have no relation to the real quality of the bark. A silvery coating on the epidermis of the bark is one of the points to which a factitious importance is attached, and renewed bark, though richer in alkaloid than natural, does not sell readily for druggists' purposes owing to the absence of the above characters, though it is readily bought by quinine manufacturers.

A specimen supposed to be one of cinchona bark can be readily identified as such by heating a small quantity in a test-tube, when a carmine-red or purple tar will be produced if the sample contain any of the cinchona alkaloids.

COMPOSITION OF CINCHONA BARKS.

Cinchona barks contain, in addition to woody fibre, starch, gum, and mineral matters:—the characteristic alkaloids; quinovin, and cinchona-red; cinchotannic and quinic acids; colouring-matters; wax, fat, and traces of volatile oil.

Water extracts only a portion of the alkaloidal constituents of cinchona bark, and a hot infusion becomes turbid on cooling from the separation of sparingly soluble cinchotannates of the alkaloids. The solution obtained by treating cinchona bark with *acidulated water* gives a white precipitate with tannin, a whitish precipitate with caustic alkalies, and a yellow crystalline precipitate with platinic chloride. Either of these precipitates yields the characteristic odour of quinoline when subjected to dry distillation.

THE ASH of cinchona barks from South American sources was found by Carles to contain a sensible amount of *copper*, but this metal was not detected by D. Hooper in the bark from trees cultivated in India (*Pharm. Jour.*, [3], xvii. 545), though in other respects the general results are in agreement. The average total ash from upwards of 300 specimens of Indian bark was found by Hooper to exceed 3 per cent. Renewed and old natural barks contain less, but the proportion never falls below 2 per cent. Young and branch barks give as much as 4 per cent. of ash, and

[1] This description refers to red cinchona bark in quills, which, in the edition of 1885, replaces the flat red bark of South America, official in the *Pharmacopœia* of 1867. The editors judiciously omit to name the place of origin, whether South America, Madras, or Ceylon; but they also omit to recognise red bark in shavings, although this is the form in which it is so most commonly met with in commerce, and notwithstanding that the shavings are often much superior, as regards the amount of quinine, to other forms.

the leaves from 5 to 6 per cent. From 24 to 27 per cent. of the ash is soluble in water, and an additional 67 to 70 per cent. in acid, leaving 5 to 6 per cent. of silica insoluble.

QUINOVIN, or CHINOVIN, is an indifferent body which appears to be a constant constituent of the cinchonas, but in a proportion seldom exceeding 2 per cent. It is dissolved on treating the bark with weak soda, and on adding hydrochloric acid to the solution is precipitated in admixture with quinovic acid and cinchona-red. Treatment with milk of lime dissolves the quinovin and quinovic acid, which are reprecipitated by an acid and separated by treatment with chloroform, which dissolves the quinovin only.[1]

Quinovin has recently been re-investigated by Liebermann and Giesel (*Berichte*, xvi. 987; *Pharm. Jour.*, [3], xvi. 987), who ascribe to it the formula $C_{38}H_{62}O_{11}$. They believe two distinct modifications to exist, α-quinovin being present in cinchona bark and β-quinovin in cuprea bark. *α-quinovin* is a white, very light, crystalline powder, quite insoluble in cold and almost insoluble in hot water, but soluble in cold caustic alkalies, lime and baryta water, and ammonia. It is difficultly soluble in chloroform, ether, and benzene. It dissolves in nearly absolute alcohol (43 : 100 at 15°), and is obtained on evaporation over sulphuric acid as a gummy mass without any tendency to crystallisation; but it separates on diluting the solution with water in rosettes of clear, very small needles. When precipitated by treating its solution in more dilute alcohol with water it is deposited in glittering white scales. The alcoholic solution of quinovin is dextro-rotatory ($S = +56{\cdot}6$), does not reduce Fehling's solution, and does not undergo fermentation with yeast. The powder is very bitter. In concentrated sulphuric acid it dissolves with orange-yellow colour and evolution of carbon monoxide. Its solution in glacial acetic acid is faintly blue, as is also the precipitate thrown down on diluting the solution with water.

β-quinovin closely resembles its isomer, but is not soluble in

[1] Quinovin is prepared by Liebermann and Giesel from a bye-product obtained when the cinchona bases are extracted from bark by means of alcohol. On distilling off the alcohol, and treating the extract with a dilute mineral acid, the alkaloids are dissolved as salts. The insoluble brown resinous matter is digested with warm milk of lime, and the filtered liquid precipitated by hydrochloric acid. The precipitate is dried and digested with alcohol, which leaves a little quinovic acid undissolved as a white powder. The brown solution is diluted with water till a precipitate commences to form, when small crystals of quinovin separate on standing. By recrystallisation from dilute alcohol it is obtained pure in the form of small glittering scales.

absolute ether or ethyl acetate, and crystallises readily from dilute alcohol in handsome scales. In nearly absolute alcohol it dissolves freely with slight evolution of heat, but after a time, even if evaporation be prevented, the greater part separates in glassy crystals containing $C_{38}H_{62}O_{11} + 5C_2H_6O$, which effloresce very rapidly in the air with loss of the alcohol. The specific rotation of β-quinovin is $+27 \cdot 9°$.

When boiled for some time with dilute sulphuric acid, or, preferably, when their concentrated alcoholic solutions are saturated with hydrochloric acid gas and allowed to stand in a closed vessel for thirty hours, both the quinovins undergo complete decomposition into quinovic acid and quinovit, a saccharoïd body apparently containing $C_6H_{12}O_4$. This substance is very hygroscopic, and has not been obtained crystalline, but may be distilled unchanged in small quantities, has a sweet taste with a bitter after-taste, is dextro-rotatory, and does not reduce Fehling's solution even after boiling with acid. It is doubtful if quinovit has been obtained pure.

Quinovic Acid, $C_{32}H_{48}O_6$, is constantly present in cinchona barks in small proportion, and forms a snow-white powder of tasteless needles or scales, quite insoluble in water, ether, or chloroform, and only very sparingly soluble in boiling alcohol or glacial acetic acid. It is best dissolved by adding ammonia to the alcohol, and may be reprecipitated by acetic acid. Quinovic acid decomposes carbonates, and is soluble in ammonia and solutions of the caustic alkalies and alkaline earths, the solutions frothing like soap. The ammonium and calcium salts crystallise from alcohol in needles; the former salt losing its ammonia by exposure to air, or on boiling its solution. On adding an acid to an alkaline solution of quinovic acid, a hydrate of quinovic acid is thrown down as a very voluminous jelly, the whole contents of the vessel solidifying. In this form quinovic acid is very soluble in ether and alcohol. From the solution, the insoluble form of the acid separates in needles on standing. Quinovic acid gives with cupric sulphate first a green colour and then a precipitate, and the latter, when washed, has a bitter metallic taste. When heated to about 300° C., quinovic acid yields pyroquinovic acid, carbon dioxide, and secondary products.

Cinchotannin or Cinchotannic Acid, $C_{14}H_{16}O_9$, is a glucoside which is an important constituent of cinchona barks, in which it exists in the proportion of 3 to 4 per cent. It may be precipitated as a lead salt from a decoction of bark—previously treated with magnesia to separate colouring-matter—by addition of lead acetate. The yellow precipitate when decomposed by sulphuretted hydrogen

yields a solution of cinchotannic acid. It is a yellow, amorphous, very hygroscopic substance, very soluble in water, alcohol, and ether; gives a green colour with ferric chloride; is precipitated by starch, albumin, gelatin, and tartar-emetic; is hydrolysed by dilute acids into glucose and cinchona-red; gives protocatechuic and acetic acids on fusion with caustic potash; yields pyrocatechol on dry distillation; and is readily decomposed in presence of excess of alkalies, with formation of cinchona-red. The cinchotannates of the alkaloids existing naturally in cinchona bark are difficultly soluble in water, but dissolve readily in acidulated water—probably with decomposition.

CINCHONA-RED or CINCHOFULVIC ACID, $C_{12}H_{14}O_7$. This is the natural colouring-matter of (red) cinchona barks, from which it may be extracted by treatment with alkalies. It is re-precipitated from its red ammoniacal solution on addition of hydrochloric acid. The solution also yields a red precipitate with barium chloride. Cinchona-red is also produced by boiling cinchotannic acid with dilute sulphuric acid, glucose being simultaneously formed. On fusing cinchona-red with potash, protocatechuic acid, $C_7H_6O_4$, is produced. Cinchona-red is insoluble in water or ether, but sparingly soluble in alcohol. It is sometimes present in red bark to the extent of 10 per cent.

QUINIC ACID or KINIC ACID, $C_7H_{12}O_6$, crystallises in well-defined hexagonal plates, fusing at 161° C. It has a strong and purely acid taste, and is soluble in 2 parts of water, less soluble in alcohol, and almost insoluble in ether. Its solutions are lævo-rotatory. When distilled with manganese dioxide and sulphuric acid, kinic acid yields quinone, $C_6H_4O_2$, which is deposited in deep yellow prisms on the cooler part of the apparatus. This reaction was proposed by Stenhouse as a test for true cinchona bark.

THE ALKALOIDS are the most important constituents of cinchona barks, in which they exist in the form of cinchotannates and quinates. The principal of them have already been fully described (page 398 *et seq.*). The official tincture and liquid extract of cinchona contain only a portion of the alkaloids of the bark used for their preparation (*Pharm. Jour.*, [3], xiv. 445, 797; xv. 453, 480).

Some kinds of cinchona bark are occasionally wholly destitute of alkaloids. Such specimens do not give a carmine-red tar when heated in a dry tube, this reaction being produced only when a cinchona base is heated with woody fibre.

The proportions of total alkaloids, as also the percentage of quinine, are extremely variable (see *Pharm. Jour.*, [3], xiv. 444, 445, 458, 797, 810; xv. 411, 453, 480), and chemical analysis

is the only means of forming an opinion as to the richness of a specimen of bark. De Vrij found the *C. officinalis* grown at Ootacamund to contain a proportion of total alkaloids varying from 11·96 per cent. (of which 9·1 per cent. was quinine) down to less than 1 per cent. Quinine is not seldom absent from barks containing certain other of the cinchona alkaloids. The highest yield of total alkaloid known is about 15 per cent. An Ootacamund bark has been found to contain 13½ per cent., the greater part being quinine. In eighty specimens of *Calisaya Ledgeriana*, from Java, Moens in 1879 found from 12·50 to 1·09 per cent. of total alkaloids, the quinine ranging from 11·6 to 0·8 per cent.

Of late years, owing to improved methods of cultivation, the proportion of quinine has sensibly increased. In the same species of cinchona, the natural bark, mossed bark, and renewed bark contain very different percentages of quinine, the last being the richest; besides which the external conditions under which the trees are grown largely affect the relative and absolute proportions of the alkaloids in the bark.

Quinine and cinchonine are the cinchona alkaloids of the most frequent occurrence. Cinchonidine is hardly less common, and it occurs very largely in Indian red bark. Quinidine is not very frequent, and is never present in large amount.

The following are analyses by D. Howard of bark from cultivated cinchona trees grown near Bagota, United States of Columbia (New Granada). The characters of the barks have been described by E. M. Holmes (*Pharm. Jour.*, [3], xxii. 875).

Species of Cinchona.	Quinine Sulphate.	Quinine.	Cinchonidine.	Quinidine.	Cinchonine.	Amorphous.	Total Alkaloids.
Thomsoniana,	5·94	4·45	0·27	0·26	0·82	0·74	6·54
Ledgeriana verde,	4·90	3·68	0·00	0·20	0·01	0·44	4·33
Negra,	7·30	5·48	0·00	trace	0·10	0·78	6·26
Morada,	3·06	2·30	0·00	0·50	0·04	0·38	3·22
Tuna,	9·04	6·78	0·40	0·18	0·38	0·42	8·16
Pombiana,	5·88	4·41	0·34	trace	0·02	0·26	5·03
Officinalis,	6·32	4·74	1·23	0·07	0·10	0·42	6·56
Succirubra,[1]	5·93	4·45	2·77	0·02	0·12	0·36	7·72
Hybrid,	3·32	2·49	1·92	trace	0·04	0·52	4·97

[1] This is by no means a typical analysis of succirubra bark (see footnote, page 447).

The following are analyses by D. Hooper, Government Quinologist, of cinchona barks grown in the Madras Government plantations, and shown at the Indo-Colonial Exhibition in 1886:—

Source of Bark.		Quinine Sulphate.	Quinine.	Cinchonidine.	Quinidine.	Cinchonine.	Amorphous Alkaloids.	Total Alkaloids.
Species.	Description.							
C. succirubra, . .	Natural	2·57	1·91	1·14	...	2·11	0·88	6·04
,, . .	Mossed	2·27	1·[illegible]	1·68	...	2·03	0·98	6·34
,, . .	Renewed	2·47	1·84	1·25	...	1·48	0·71	5·28
,, . .	Branch	1·85	1·38	1·59	...	2·28	1·16	6·41
,, . .	Root	1·66	1·24	1·43	0·41	0·77	1·27	5·12
,, . .	Renewed (shavings)	3·09	2·30	2·06	...	1·16	1·45	6·97
C. robusta,[1] . .	Natural	1·92	1·43	1·58	...	2·08	0·31	5·40
,, . .	Mossed	2·58	1·92	0·77	...	3·16	0·35	6·20
,, . .	Renewed	5·92	4·40	0·51	...	2·54	1·65	9·10
,, . .	Branch	2·20	1·64	1·17	...	2·71	0·50	6·02
C. micrantha, . .	Natural	...	...	1·92	...	...	0·40	2·32
,, . .	Renewed	trace	trace	1·12	...	2·45	1·02	4·54
,, . .	Branch	...	...	1·60	...	...	0·45	2·05
C. Calisaya, . .	Natural	1·62	1·21	2·13	...	2·32	0·29	5·95
,, . .	Branch	0·79	0·59	1·93	...	0·73	0·48	3·73
C. Anglica,[1] . .	Natural	1·09	0·81	1·49	0·29	0·88	0·44	3·91
,, . .	Branch	trace	trace	2·04	0·25	...	0·36	2·65
C. Ledgeriana, .	Natural	7·38	5·49	0·82	...	1·33	0·88	8·52
,, . .	Branch	2·97	2·21	1·07	...	0·49	0·50	4·27
C. Javanica, . .	Natural	...	...	2·64	1·32	...	0·48	4·44
,, . .	Branch	...	...	1·49	1·43	...	0·45	3·37
C. officinalis, . .	Natural	3·72	2·77	0·39	0·16	1·57	0·50	5·39
,, . .	Mossed	4·57	3·40	0·45	0·20	1·50	0·62	6·17
,, . .	Renewed	5·66	4·21	0·65	0·22	0·85	0·70	6·63
C. paludiana, . .	Natural	0·05	0·04	0·39	...	0·10	0·43	0·96
,, . .	Renewed	0·68	0·51	0·28	...	1·19	0·87	2·85
C. Pitayensis, . .	Natural	3·14	2·34	1·93	1·10	0·56	0·39	6·32
,, . .	Mossed	5·12	3·81	1·91	0·63	0·95	0·37	7·67
,, . .	Renewed	3·36	2·50	2·33	0·78	0·52	0·55	6·68
C. Humboltiana, .	Natural	3·01	2·24	0·49	trace	1·55	0·90	5·18
,, .	Renewed	1·72	1·28	0·43	...	0·64	1·07	3·42

[1] *Cinchona robusta* is a hybrid or cross between *C. succirubra* and *C. officinalis*, and *C. Anglica* between *C. succirubra* and *C. Calisaya* (W. T. Thiselton Dyer, *Pharm. Jour.*, [3], xv. 481).

Analyses of a number of cinchona barks from Madras have been published by B. H. Paul (*Pharm. Jour.*, [3], xiv. 666). D. Hooper (*Year-Book Pharm.*, 1888, page 430) gives the following as the percentage proportions of alkaloids in *typical* barks from trees grown on the plantations of the Madras Government: [1]—

[1] In commenting on these results, B. H. Paul strongly deprecated the preference given to the red bark over that of the crown and Calisaya barks,

	Bark from C. succirubra.[2]	Crown Bark from C. officinalis.[2]	Hybrid Barks.
Quinine, ...	1·40	2·93	2·16
Cinchonidine, . . .	2·25	1·40	1·82
Quinidine, ...	...	0·08	0·04
Cinchonine, ...	1·92	0·42	1·17
Amorphous alkaloids, . .	0·68	0·42	0·56
Total, . . .	6·25	5·25	5·75

Hooper gives the following as the average centesimal composition of the alkaloids from numerous species of the above barks:[1]—

	Red Barks.[2]	Crown Barks.	Hybrid Barks.
Quinine, ...	22·2	55·9	41·2
Cinchonidine, . . .	36·1	26·7	40·9
Quinidine, ...	...	1·5	0·5
Cinchonine, ...	30·9	8·0	9·7
Amorphous alkaloids, . .	10·8	7·9	7·7
Total, ...	100·0	100·0	100·0

which had acted prejudicially on all concerned. This prejudice had extended to the *B. Pharmacopœia*, with the result that "every bark preparation that appeared there was, in fact, an officially adulterated article," and contained for every unit of quinine, the only really valuable constituent, 2, 3, or 4 per cent. of the comparatively valueless ones (*Year-Book Pharm.*, 1888, page 440). The typical crown bark, of which the analysis is given in the text, Paul regarded as of only inferior quality, the proportion of alkaloids yielded by crown bark of any value being from 3 to 5 per cent. of sulphate of quinine, and something less than 1 per cent. of cinchonidine. In the red bark these proportions were reversed, the quinine being usually 1½ per cent., with 3, 4, and 5 per cent. of cinchonidine. Red bark had become a drug in the market, and almost worthless as a source of quinine. In replying to these criticisms (*Pharm. Jour.*, [3], xix. 504), Hooper pointed out that the fifty crown barks of which the analyses were given were undoubtedly of a typical character; barks of the richer species, as *angustifolia*, were purposely omitted; and that mossed and renewed barks are also eliminated.

[1] See foregoing footnote.

[2] The mixed total alkaloids of red bark have been introduced into commerce under the name of "Quinetum." This preparation is completely soluble in warm, strong alcohol; 3·1 grammes dissolved in 10 c.c. of normal hydrochloric

Assay of Cinchona Barks.

The complete assay of the various species of cinchona bark, with the view of ascertaining the proportion of the different alkaloids contained in them, is a process at once important and difficult. A great many methods have been proposed, but very few can be trusted to yield accurate results when employed by chemists unused to them. Again, a process which is suitable when quinine is the chief alkaloid present becomes difficult of application when the cinchonidine is in excess. Unfortunately, also, certain processes which are extensively employed by professed quinologists are kept strictly secret.

In choosing a process of assaying cinchona bark, due consideration should be given to the kind of information required. Thus, a pharmacist desiring to know the alkaloidal strength of his bark will require a less accurate and elaborate process than a manufacturer buying bark for the extraction of quinine. Again, in some cases it is sufficient to determine the percentage of total alkaloids, while in others it is very important to ascertain the proportion of crystallised sulphate of quinine which the bark is capable of yielding. On this account, it is desirable to discuss the determination of the total alkaloids and of the actual quinine separately.

a. The *British Pharmacopœia* of 1885 prescribes the following standard of quality and method of assaying[1] red cinchona bark :—

"*Test.*—When used for purposes other than that of obtaining the alkaloids or their salts, it should yield between 5 and 6 per cent. of total alkaloids, of which not less than half shall consist of quinine and cinchonidine,[2] as estimated by the following methods :—

"1. *For Quinine and Cinchonidine.*—Mix 200 grains of red cinchona bark, in No. 60 powder, with 60 grains of hydrate of

acid should give a clear solution, which, on addition of 2 grammes of Rochelle salt must yield a precipitate equal in weight, after drying, to *at least* 65 per cent. of the quinetum taken.—(From the Unofficial Formulary of the Dutch Society for the Advancement of Pharmacy, *Pharm. Jour.*, [3], xii. 662.) "Quinetum sulphate" occurs in commerce in a perfectly crystallised form.

[1] Based on a method devised by E. R. Squibb (*Ephemeris*, i. 106).

[2] This is not a very exacting requirement. Unfortunately no indication is given of the proportion of actual quinine which should be present. Consequently, one bark may have double the intrinsic value of another, and yet both be fairly up to the B.P. standard. It is quite possible for a bark to contain the required proportion of total alkaloid, of which one-half shall consist of cinchonidine and quinine, but still only traces of the last alkaloid to be present. As the shavings are excluded, and the established prejudice as to the appearance of quills tends to favour the use of natural rather than the richer renewed bark, the general effect is to promote the use of the least

calcium; slightly moisten the powders with half an ounce of water; mix the whole intimately in a small porcelain dish or mortar; allow the mixture to stand for an hour or two, when it will present the characters of a moist, dark brown powder, in which there should be no lumps or visible white particles. Transfer this powder to a six-ounce flask, add three fluid ounces of benzolated amylic alcohol,[1] boil them together for about half an hour, decant and drain off the liquid on to a filter, leaving the powder in the flask; add more of the benzolated amylic alcohol to the powder, and boil and decant as before; repeat this operation a third time; then turn the contents of the flask on to the filter, and wash by percolation with more of the benzolated amylic alcohol until the bark is exhausted. If, during the boiling, a funnel be placed in the mouth of the flask, and another flask filled with cold water be placed in the funnel, this will form a convenient condenser which will prevent the loss of more than a small quantity of the boiling liquid. Introduce the collected filtrate, while still warm, into a stoppered glass separator; add to it 20 minims of diluted hydrochloric acid, mixed with 2 fluid drachms of water; shake them well together, and when the acid liquid has separated this may be drawn off, and the process repeated with distilled water slightly acidulated with hydrochloric acid, until the whole of the alkaloids have been removed. The acid liquid thus obtained will contain the alkaloids as hydrochlorates, with excess of hydrochloric acid. It is to be carefully and exactly neutralised with ammonia while warm, and then concentrated to the bulk of 3 fluid drachms. If now about 15 grains of tartarated soda, dissolved in twice its weight of water, be added to the neutral hydrochlorates, and the mixture stirred with a glass rod, insoluble tartrates of quinine and cinchonidine will separate completely in about an hour; and these collected on a filter, washed, and dried, will contain eight-tenths of their weight of the alkaloids, quinine and cinchonidine, which, divided by 2, represents the percentage of those alkaloids. The other alkaloids will be left in the mother-liquor."

"2. *For Total Alkaloids.*—To the mother-liquor from the preceding process add solution of ammonia in slight excess. Collect, wash, and dry the precipitate,[2] which will contain the other alkaloids. The weight of this precipitate, divided by 2 and

valuable kinds of bark for pharmaceutical purposes. In the present *Pharmacopœia* definition, the quinine standard of cinchona bark is reduced much below that of the 1867 edition, and only corresponds to a content of about 1 per cent. of quinine.

[1] Prepared by mixing 3 volumes of benzene with 1 of amylic alcohol.

[2] It would be better to extract the alkaloids with chloroform.

added to the percentage weight of the quinine and cinchonidine, gives the percentage of total alkaloids."

b. The following method of determining the total alkaloids of cinchona bark is that of J. E. De Vrij, with certain modifications suggested by A. B. Prescott and J. Muter. It is practically the official process of the *United States Pharmacopœia*, and is applicable to all varieties of bark. Twenty grammes of the finely-powdered bark, weighed after drying at 100° C., is thoroughly mixed with 5 grammes of quick-lime and 50 c.c. of water. The mixture is then dried at a very gentle heat, not above 70° to 80° C. When dry, it is transferred to a flask fitted with an inverted condenser, and boiled with 200 c.c. of the strongest rectified spirit.[1] The liquid is allowed to cool, and is then passed through a filter six inches in diameter, and the residue is again boiled with 100 c.c. of alcohol, and then washed twice with alcohol, using 50 c.c. each time. The filtrate is next rendered slightly acid by dilute sulphuric acid, and, after allowing any precipitate of calcium sulphate to subside, the liquid is passed through a very small filter, which is washed with a little alcohol. The filtrate is evaporated or distilled till the alcohol is expelled, cooled, and again passed through a small filter, the precipitate, consisting of quinovic acid and fatty matter, being washed with water slightly acidulated with sulphuric acid. The filtrate, which contains the alkaloids in the form of acid sulphates, is then concentrated to about 50 c.c. or less, and transferred to a separator of 100 to 150 c.c. capacity. Soda is next added in decided excess, and the liquid containing the separated alkaloids then shaken without delay with 30 to 40 c.c. of previously washed chloroform. After a few minutes' agitation, the liquid is left at rest till the chloroform has completely separated from the aqueous layer. The lower stratum is then tapped off, and the watery liquid agitated three times more with chloroform, using from 25 to 30 c.c. on each occasion. The mixed chloroformic solutions are then distilled to a small bulk, the residual liquid evaporated to dryness, and the residue dried in the water-oven till constant in weight. The amount so found represents the total alkaloids in the 20 grammes of the bark taken. Cinchonine and cinchonidine readily become anhydrous at 100°, and quinine may be trusted to do the same. Quinidine retains 2 aqua in the water-oven, but the proportion in which this base occurs is too

[1] The spirit may be methylated, but should be previously dehydrated to about 93 per cent. by being kept in contact with freshly-ignited potassium carbonate. A Soxhlet's tube or equivalent arrangement might probably be advantageously employed for the alcoholic treatment described in the text.

small to affect appreciably the accuracy of the assumption that the alkaloids are weighed in the anhydrous state. If preferred, however, the temperature may be raised to 115° C.[1]

For the assay of *yellow* cinchona bark, ether may be substituted for the chloroform employed in the above process.

c. The following method of assay is due to Prollius (*Archiv d. Pharm.*, ccix. 85, 572), with precautions suggested by De Vrij, Biel, and others. It is practically the process of the *German Pharmacopœia* (1882):—Prepare a mixture of 85 parts of ether (sp. gr. 0·724 to 0·728), 10 parts of alcohol (sp. gr. 0·830 to 0·834), and 5 parts of ammonia (sp. gr. 0·960), all *by weight*, making 100 parts in all. Treat 10 or 20 grammes (according to its supposed richness) of the previously dried and *very finely-powdered* cinchona bark in a tared glass-stoppered bottle with twenty times its weight of the above solvent-mixture, observe the exact weight of the bottle and its contents, and agitate at intervals during four hours. If any loss of weight occurs, add sufficient of the solvent-mixture to restore it, agitate and weigh again. Carefully decant into a flask as much of the solution as can be poured off perfectly clear, and ascertain the quantity taken by re-weighing the stoppered bottle. Distil off the ether, evaporate the residual liquid in a tared beaker at 100°, and weigh the residue when thoroughly dry. Then:—

$$\frac{\text{Weight of solvent-mixture employed} \times \text{weight of residue}}{\text{Weight of alkaloidal solution decanted}} = \left\{\begin{array}{l}\text{total crude alkaloids}\\ \text{in bark taken.}\end{array}\right.$$

The crude alkaloids thus obtained are dissolved in dilute hydrochloric acid, the solution filtered, and the filtrate made alkaline with caustic soda and repeatedly agitated with chloroform, which is separated, evaporated, and the residual alkaloids weighed after drying at 100° in the usual way. De Vrij found the purified alkaloids so obtained from a red Java bark to be 83·5 per cent. of the total crude alkaloids previously extracted.

[1] With a few modifications of minor importance, the method described in the text is that used by most quinologists. One well-known authority prefers to work on a very large quantity of the bark (about 2 lbs.). Having treated with lime, alcohol, and acid in the manner described in the test, he precipitates the aqueous solution of the sulphates with soda, filters, washes slightly, dissolves the precipitate in acetic acid, and filters from any undissolved colouring-matter. The filtrate is divided into two equal parts, A and B. A is precipitated by ammonia, filtered, and the filtrate shaken with chloroform, which is then used to dissolve off the alkaloids from the filter. The solution is evaporated, and the total alkaloids weighed, after drying at 115° C. B is treated in a manner similar to A, but the chloroform is replaced by ether. The alkaloid thus dissolved is called "quinine," the difference between that and the total alkaloids being the "other alkaloids."

d. The following method for the estimation of the total alkaloids of cinchona bark is that of Hager. The accuracy of the method has been confirmed by O. Medin (*Zeit. Anal. Chem.*, viii. 477; ix. 447):—Ten grammes of the dried and finely-powdered bark are treated for a short time with 100 c.c. of water and 10 grammes of caustic potash solution of 1·35 specific gravity. The mixture is then heated and kept at the boiling-point for a quarter of an hour. Fifteen grammes' weight of diluted sulphuric acid (sp. gr. 1·115) is next added, and the whole boiled for twenty minutes. After cooling, both liquid and residue are transferred to a measuring cylinder, and diluted with water till the whole has a volume of 110 c.c.[1] The liquid is then passed through a dry filter, and 60 c.c. of the filtrate (= 6 grammes of bark), mixed with 50 c.c. of a cold, saturated, aqueous solution of picric acid. After standing for half an hour the precipitated picrates are filtered off, washed with a little cold water, dried at 100°, and weighed. The product contains 42·5 per cent. of its weight of alkaloids, calculated as quinine. A preferable plan is to suspend the washed precipitate in cold water, add excess of caustic soda, and agitate with chloroform. The chloroformic solution of the alkaloids is then treated as in process *b*. The picric acid method of assaying cinchona barks is said to be accurate, easy, and expeditious.

Separation of Cinchona Bases.

The separation of the alkaloids of cinchona and allied barks is an extremely complex operation, and as respects the rarer alkaloids outside the scope of this work. But the accurate separation even of the commoner alkaloids, such as is frequently required for commercial purposes, is very difficult, and its accurate performance presents special obstacles to an inexperienced analyst. In some cases it is sufficient to determine the proportion of crystallisable quinine, which may be effected as described below, but in other cases it is necessary to determine also the cinchonine, cinchonidine, and occasionally the quinidine, quinamine, and amorphous alkaloids. For the separation of quinine from the admixed alkaloids, ether is usually employed, but it must be remembered that the separation effected by this solvent is not an absolute one, all the free cinchona bases being more or less soluble in ether, especially in the presence of quinine. The anhydrous sulphates of quinine and cinchonidine are almost insoluble in chloroform free from alcohol (see page 430), but in presence of sulphate of cinchonine or quinidine sensible

[1] This is allowing 100 c.c. for the liquid, and 10 c.c. for the bulk of the residual woody fibre, &c.

quantities pass into solution. Crystallisation of the quinine sulphate from water affords a simple and fairly accurate mode of separation, which has the advantage of being similar to the process employed by the manufacturer, and hence is regarded by many as furnishing the best proof of the yield likely to be obtained in practice. The following method of separating the quinine in the form of sulphate is described by J. Muter (*Analyst*, v. 223):—Treat the total alkaloids, or the ether-residue from 20 grammes of bark, with warm distilled water slightly acidulated with dilute sulphuric acid, till the mixture is perceptibly acid. Add water to make 70 c.c. for each 1 gramme of alkaloids taken, and then very dilute soda with constant stirring till the liquid is exactly neutral, with a faint tendency to acidity. Digest the liquid at 85° C. for five minutes; then cool, and leave at 15° C. for one hour. Filter the liquid through a small double filter (2¾ inches diameter), the two filters being previously trimmed to equal weight, and receive the filtrate in a graduated cylinder. Wash carefully with water at 15° C. till the filtrate and washings measure 90 c.c. for each 1 gramme of the mixed alkaloids. The filter and contents are now completely dried at 100° C., and weighed, the second filter being used as a counterpoise. To the weight in grammes add ·000817 gramme for each c.c. of filtrate and washings. The sum divided by 0·855 gives the corresponding amount of crystallised sulphate, and this number multiplied by 5 gives the crystallised quinine sulphate obtainable from 100 grammes of dried bark.

The quinine sulphate so obtained is apt to contain cinchonidine sulphate, and should be tested for this admixture as directed on page 412. The remaining alkaloids may be recovered from the mother-liquors by concentrating the liquid somewhat, adding soda in excess, and agitating with chloroform. On evaporating the chloroform, the bases will be obtained in a solid state, and may be separated as described on page 459.

The following scheme for the separation of the principal cinchona bases is founded on a method described by De Vrij (*Pharm. Jour.*, [3], ii. 642). The process requires a considerable weight of alkaloids, and does not yield strictly accurate results. Traces of quinidine and cinchonidine are dissolved by the ether, and are only recovered on treatment of the amorphous alkaloids with a limited quantity of ether as directed.[1] In presence of much quinine the solubility of cinchonidine in ether is notably increased.

[1] The solubility of the cinchona bases in ether at 15° C. is given by A. B. Prescott as being:—for quinine, 1 : 25; quinidine, 1 : 30; cinchonidine, 1 : 188; and for cinchonine, 1 : 371. The amorphous cinchona alkaloids are readily soluble in ether.

SEPARATION OF CINCHONA ALKALOIDS.

A weight of not less than 2, and preferably 5, grammes of the mixed alkaloids in a free state is finely powdered,[1] and treated in a closed tube with ten times its weight of ether (free from alcohol). The mixture is well shaken and left at rest for twelve hours, when it is filtered, and the residue washed with a small quantity of ether.

A. The Residue is dried and weighed. It may contain *cinchonine*, *cinchonidine*, and *quinidine*. It is dissolved in a slight excess of dilute acetic acid, and the solution rendered neutral to litmus by cautious addition of soda. The cinchonidine is then precipitated as tartrate, the quinidine as hydriodide, and the cinchonine as the free alkaloid, the operations being conducted exactly as described on page 459, with the exception that quinine and amorphous alkaloids having been previously removed, the processes and calculations necessitated by the their presence may be omitted.

B. The Ethereal Solution is evaporated to dryness, and the residue weighed. It consists of *quinine*, *amorphous alkaloids*, and *quinamine*, with heavy traces of *quinidine* and *cinchonidine*. It is dissolved in 10 parts of proof spirit, acidulated with $\frac{1}{20}$ of sulphuric acid. To this solution an alcoholic solution of iodine is gradually added as long as a precipitate is produced. Excess of iodine must be carefully avoided. In presence of much quinine, a black precipitate of herepathite is immediately produced, but if the quantity is small some time is required for its appearance. In such a case only a small quantity of iodine solution must be added, and the liquid well stirred, and left twelve hours. The precipitate is filtered off, and washed with strong alcohol.

C. The Precipitate consists of herepathite. It is dried at 100° C., weighed. The weight, multiplied by ·55055, gives the quantity of *quinine* in the mixed alkaloids operated upon. The precipitate may also be treated with sodium thiosulphate or sulphurous acid and the alkaloid liberated by ammonia, extracted with ether, and titrated or weighed.

D. The Solution is treated with sulphurous acid till colourless, and then carefully neutralised with caustic soda. The alcohol is evaporated off, and the liquid treated with excess of soda or ammonia, and agitated with chloroform. The residue left on evaporating the chloroform consists of *amorphous alkaloids*, with considerable traces of *quinidine* and *cinchonidine*. The two latter will remain undissolved on treatment with a limited quantity of ether, and the amorphous alkaloids may be examined by De Vrij's test, described on page 435.

[1] It is not always an easy matter to obtain the mixed alkaloids in a condition of fine powder, especially if their total amount has been determined by evaporating a chloroformic or other solution in a flask. For the treatment of such residues, E. R. Squibb (*Ephemeris*, i. 111) recommends that 5 grammes of glass, which has been reduced in a mortar to a mixture of coarse and fine powder, should be placed in the flask containing the alkaloid, from 5 to 10 grammes of bark, this being followed by 5 c.c. of ether, of specific gravity not higher than 0·725. The flask is corked and shaken vigorously so as to grind up the alkaloidal residue and mix it thoroughly with the glass. Then pass the liquid through a very small filter (2·8 inches) previously wetted with ether, and wash with drops of ether delivered from a pipette till the filtrate measures 10 c.c. Change the receiver and continue the washing till another 10 c.c. has been collected. Then evaporate each portion to dryness, and correct the weight left by the first (quinine, &c.) by that of the residue from the second, which represents the traces of quinidine, cinchonidine, &c., soluble in 10 c.c. of ether.

The precipitation of the quinine as herepathite is stated by David Howard to give accurate results in skilful hands; but, instead of throwing down the quinine from a sulphuric acid solution by tincture of iodine, De Vrij recommends, in his more recent papers, the use as a precipitant of the iodosulphate of the amorphous cinchona bases commercially known as "quinoïdine." This forms a readily soluble iodosulphate, and by employing a previously prepared solution of it any error from the formation of periodised iodosulphate of quinine is avoided.[1] De Vrij directs

[1] *Pharm. Jour.*, [3], vi. 461; xii. 601. One part of commercial "quinoïdine" is heated on a water-bath with 2 parts of benzene, whereby the quinoïdine is partly dissolved. The cold, clear benzene-solution is shaken with excess of dilute sulphuric acid, an aqueous solution of the acid sulphate of quinoïdine being thus obtained. The amount of alkaloid is then determined in a small portion of this solution, and the rest is slowly treated with 1 part of iodine and 2 of potassium iodide dissolved in water for every 2 parts of amorphous alkaloid known to be present. The iodine solution must be added very gradually, with vigorous stirring, so that no part of the quinoïdine solution shall come in contact with excess of iodine. A flocculent, orange-coloured precipitate of iodosulphate of quinoïdine is formed, which by slight elevation of temperature coagulates to a dark brownish-red resinoid body. The yellowish liquid is poured off, and the precipitate heated to 100° with water, when the liquid is poured away. The adhering moisture is evaporated off at 100° C., when the iodosulphate remains as a soft and tenacious mass, which becomes brittle on cooling. One part of this substance is dissolved by heating with 6 parts of alcohol of 92 to 95 per cent. The solution is allowed to cool, filtered, evaporated to dryness, and the residue dissolved in 5 parts of cold alcohol. When filtered, the solution thus obtained is ready for use.

In using this solution for the determination of crystallisable quinine in a mixture of cinchona bases (as free as possible from cinchonidine), 1 part by weight of the alkaloid is dissolved in 20 parts of alcohol of 92 to 95 per cent., containing 1·5 per cent. of sulphuric acid (H_2SO_4), which amount is sufficient to convert the bases into acid sulphates. The solution is then diluted with 50 parts of unacidulated alcohol. To this liquid, at the ordinary temperature, the iodosulphate of quinoïdine is added drop by drop from a burette, with constant stirring, as long as a dark brownish-red precipitate of herepathite is formed. As soon as all the quinine has been precipitated, and a slight excess of the reagent has been added, the liquor acquires an intense yellow colour. The beaker is now covered and heated on a water-bath till the liquid begins to boil, and all the precipitate is dissolved, when the liquid is allowed to cool. After standing twelve hours, the beaker is weighed with its contents. The liquid is next passed through a small filter, leaving the crystals in the beaker, which is then again weighed to ascertain the weight of the liquid. The crystals on the filter are washed back into the beaker, and as much alcohol added as is necessary to dissolve the crystals at the boiling-point. When quite cold the beaker is again weighed, the recrystallised herepathite collected on a small filter, and the empty beaker again

the addition of the reagent to the solution of the mixed alkaloids of cinchona bark, but it has been pointed out by Christensen, Shimoyama, and others (*Pharm. Jour.*, [3], xii. 441, 1016; xvi. 205; xvii. 654), that cinchonidine, if present in notable quantity, is liable to be precipitated along with the quinine, and hence this base should be separated as completely as possible by a previous ether-treatment, as directed on page 455. The use of the iodo-sulphate of quinoïdine prevents any subsequent isolation of the amorphous alkaloids of the bark under examination.

Instead of converting the quinine in the ethereal solution B into herapathite, David Howard (*Watts' Dict. Chem.*, 2nd ed., ii. 177) agitates the ethereal liquid with excess of dilute sulphuric acid, and, after heating to boiling, adds dilute ammonia till neutral to litmus, using no more water than is necessary. On cooling, the *quinine* crystallises out almost entirely as sulphate, which salt is almost insoluble in a cold solution containing ammonium sulphate. The crystals are filtered off, washed with a little cold water, pressed between blotting-paper, and dried at 100° C. 73·4 parts of the anhydrous salt represent 100 parts of the crystallised sulphate. The product should be tested for cinchonidine (page 412), which may be present in small quantity. The alkaloids existing in the mother-liquor from the quinine sulphate are then recovered by concentrating the liquid somewhat, adding soda in excess, and shaking with chloroform. The bases are extracted from the separated chloroform by dilute acetic acid, and the solution treated as in A.

The mixed alkaloids of yellow cinchona bark consist chiefly of quinine, and hence the portion soluble in ether represents the most useful constituents of the bark. Pale and red barks, on the other hand, contain a considerable proportion of alkaloids insoluble

weighed. The difference indicates the weight of the mother-liquor, which is added to that of the main quantity.

The recrystallised herepathite obtained as above is washed on the filter with a saturated solution of herepathite in alcohol of 92 per cent. The adhering liquid is removed as far as possible by pressing the folded filter and its contents between blotting-paper, and the filter is then air-dried. The precipitated herepathite is then detached from the filter, dried at 100° till constant, and weighed. The amount found is corrected by the addition of that remaining in solution, as ascertained by calculation from the weight of the mother-liquor. One hundred grammes of alcohol of 92 per cent. dissolve ·133 gramme of herepathite at 24·5° C., and ·125 gramme at 16° C.

The weight of herepathite found, multiplied by ·55055 gives the anhydrous, or by 0·7409 the corresponding weight of crystallised, sulphate of quinine. Instead of drying the recrystallised herepathite, it might probably be titrated with standard sodium thiosulphate solution. 21·58 parts of iodine thus found represent 100 parts of herepahite.

or sparingly soluble in ether. Hence the use of chloroform in the general process for assaying cinchona barks (see page 451).

In some cases, the alkaloids soluble in ether are contaminated to a considerable extent with colouring matter. In this event, the following is a good method of obtaining colourless quinine sulphate:—The ether-residue is dried thoroughly and weighed. It is then dissolved in 30 c.c. of absolute alcohol, and decinormal sulphuric acid cautiously added from a burette, till the liquid is neutral or *very faintly acid to litmus-paper* or methyl-orange. Each c.c. is equivalent to 0·324 gramme of anhydrous alkaloids. The liquid is next evaporated nearly to dryness, and a measure of decinormal sulphuric acid added equal to that previously required for neutralisation. Thirty c.c. of hot water are added, and the liquid boiled till complete solution results. Purified animal charcoal is next added, in quantity equal to the weight of the ether-residue, the liquid heated on the water-bath for twenty minutes, filtered, and the residue washed twice with boiling water acidulated with sulphuric acid. The filtrate is brought to a concentration of 70 c.c. for each 1 gramme of ether-residue taken, and then cautiously neutralised with caustic soda, and further treated as described on page 451.

Instead of commencing the separation of the alkaloids by ether, Moens recommends that the neutral solution of the mixed alkaloids should be treated with excess of solution of potassium sodium tartrate (Rochelle salt), which throws down the quinine and cinchonidine as tartrates. The same procedure is adopted in the *British Pharmacopœia* (see page 450). The precipitated tartrates are washed with a little cold water, decomposed by excess of alkali, and the quinine and cinchonidine separated by ether; the quinine dissolved being either directly weighed, or, preferably, converted into sulphate and tested for cinchonidine (page 412).

The estimation of the relative proportions of quinine and cinchonidine in the mixed tartrates, by observing the optical activity (page 415), has been recommended by several chemists, but in practice it is difficult to obtain the alkaloids in a sufficiently pure condition to render the results trustworthy.

The following method for the separation of the cinchona bases insoluble, or nearly insoluble, in ether may be applied to the residue left on treatment of the mixed alkaloids with ether, as in De Vrij's process (page 454). It may also be applied directly to the mixed alkaloids extracted from a sample of bark, in which case it may be carried on simultaneously with Muter's process for the production of crystallised quinine sulphate as described on page 454.

Analysis of Cinchona Bases. Separation of Cinchonine, Cinchonidine, and Quinidine.

The mixed alkaloids extracted from the bark, or from the filtrate from the crystallised quinine sulphate by treatment with soda and chloroform, or the residual alkaloids left on treating the total alkaloids with ether (see page 455), are dissolved in dilute sulphuric acid, and the solution exactly neutralised by soda. A saturated solution of Rochelle salt is next added in excess, the liquid cooled to 15° C., and repeatedly stirred during one hour. Crystalline streaks in the track of the glass rod consist of c i n c h o n i d i n e (or quinine) t a r t r a t e. The precipitate is collected on a double tared filter, and washed first with a 5 per cent. solution of Rochelle salt and then with a little cold water, the filtrate and washings being collected in a graduated cylinder.

T h e P r e c i p i t a t e is dried at 100° to 105° C. and weighed, the outer filter being used as a counterpoise. The amount found is corrected by adding ·00083 gramme for each 1 c.c. measured by the filtrate and wash-water. The sum multiplied by 0·797 gives the weight of *cinchonidine.* If quinine has not previously been separated, the amount of crystallised sulphate found must be multiplied by ·915, and the product subtracted from the weight of the tartrate before calculating it to cinchonidine. A preferable plan is to dissolve the precipitate off the filter with dilute sulphuric acid, add ammonia, and extract with ether, weighing or titrating the alkaloid. (See also author's method described on next page.)

A. T h e F i l t r a t e is concentrated to its original bulk, cooled, a drop of dilute acetic acid added, and then excess of a saturated solution of potassium iodide (free from any alkaline reaction). The liquid is left for two hours at 15° C., being frequently stirred. Any streaks in the track of the glass rod are produced by q u i n i d i n e h y d r i o d i d e. The liquid is filtered on a double counterpoised filter, and the precipitate cautiously washed with cold water.

T h e P r e c i p i t a t e is dried at 100° and weighed. Its weight is corrected by the addition of ·00077 gramme for each 1 c.c. of filtrate and washings (B). The sum, multiplied by ·7168, gives the *quinidine;* or the precipitate may be decomposed by ammonia, the alkaloid extracted by ether, and titrated or weighed. (See next page also.)

B. F i l t r a t e is measured and made distinctly alkaline with caustic soda, and the precipitated *cinchonine* is extracted by agitation with chloroform, which is separated, evaporated, and the residue weighed or titrated. The weight found is corrected by deducting ·00052 for each 1 c.c. measured by filtrate A, and ·00066 for each c.c. of filtrate B. Any *amorphous alkaloid* may be dissolved out by spirit of 0·94 specific gravity.

The foregoing process, with experience, gives very good results, the sum of the separated alkaloids frequently amounting to 99 per cent. of the mixed bases operated on. It is well suited for the assay of Indian barks. The least satisfactory part of the process is the separation of the cinchonine from the amorphous bases by dilute spirit. A cautious employment of ether would perhaps be preferable. If the process of separation be conducted simultaneously with the determination of the crystallised quinine sulphate in another portion (page 454), the whole analysis can be completed in about six hours.

According to Hielbig (*Pharm. Zeitsch. f. Russland*, 1888; *Analyst*, xiii. 207) the presence of much quinidine prevents the complete precipitation of the cinchonidine and quinine as tartrates; while the precipitate with potassium iodide, if tenacious or resinous instead of crystalline, contains cinchonine, with or without quinidine. (It seems more probable that the resinous precipitate consists of the hydriodides of amorphous alkaloids, which can be kept in solution by moderate addition of alcohol.)

The directions in the foregoing table can be modified with considerable saving of time by titrating the alkaloids and their salts instead of weighing them. Thus, for the determination of the *cinchonidine*, the washing of the precipitated tartrate with cold water should be omitted, and the filter containing the precipitate and the adhering Rochelle salt solution immersed in boiling water. A drop of phenolphthaleïn solution is then added, and the liquid titrated with $\frac{N}{20}$ caustic alkali. As Rochelle salt is perfectly neutral to phenolphthaleïn, and as tartrate of cinchonidine (and of quinine) acts just like an equivalent amount of free tartaric acid, the weight of cinchonidine can be readily calculated from the measure of standard alkali used. Each 1 c.c. of $\frac{N}{20}$ NaHO neutralised represents 0·0147 gramme of cinchonidine (or other alkaloid) precipitated as tartrate (A. H. Allen).

An exactly similar method is applicable to the treatment of the precipitate produced by potassium iodide. This should be washed with a little of the precipitant instead of with water, and then immersed together with the filter in boiling water. On titrating with $\frac{N}{20}$ alkali and phenolphthaleïn each 1 c.c. of the standard solution required represents 0·0162 gramme of *quinidine* precipitated as hydriodide.[1]

The chloroformic solution of the *cinchonine* may be directly titrated with standard acid and methyl-orange (see p. 131) instead of being evaporated to dryness; but, of course, the amount found will include any amorphous alkaloid also extracted by the chloroform.

[1] This procedure does not dispense with the necessity of making a correction for the amount of quinidine lost in the mother-liquor and washings.

BERBERINE AND ITS ASSOCIATES.

Berberine is an alkaloid occurring in a very large number of plants, in many cases in association with one or more of the alkaloids, berbamine, oxyacanthine, hydrastine, canadine, &c. It is the only natural basic colouring matter receiving practical application as a dye.

The principal sources of berberine and the associated alkaloids are the roots of the following plants:—

PLANT.	ALKALOIDS, &c.
Berberis vulgaris (Barberry),[1] .	Berberine; oxyacanthine; berbamine; and at least two other alkaloids (Hesse).
Berberis aquifolium, . . .	Berberine, 2·35 per cent.; oxyacanthine, 2·82 per cent.
Coptis trifolia, ...	Berberine, 4 per cent.
Coptis teeta (India), ...	Berberine, 8½ per cent.; coptinine (crystallisable; Gross).
Hydrastis Canadensis (Golden seal),	Berberine, 1·3 to 1·8 per cent.; hydrastine, 1·5 per cent.; canadine; xanthopuccine; &c. Also meconin and phytostearin.
Jateorhiza Calumba or *Cocculus palmatus* (Calumba root),	Berberine; columbic acid; and the neutral principle columbin.
Menispermum Canadense, . .	Berberine; oxyacanthine; menispermine; menispine.

Berberine has also been found in Woodumpar, a yellow dye-wood from Upper Assam; in St John's wood, from Rio Grande; in *Berberis aristata, Caulophyllum thalictroïdes, Coscinium fenestratum* (Ceylon Calumba wood), *Cœlocline polycarpa, Podophyllum pellatum, Xanthorhiza apiifolia*, and *Xanthoxylum clava-Hercules.* Hydrastine occurs also in *Stylophorum diphyllum.*

Berberine. $C_{20}H_{17}NO_4$; or $C_{18}H_{11}(O.CH_3)_2NO_2$.

Berberine is isolated from the root of *Hydrastis Canadensis* by boiling with water, evaporating the decoction to an extract, and exhausting with strong alcohol. One-fourth of its volume of water is added to the filtered alcoholic solution, the alcohol distilled off, and the residue treated with dilute sulphuric acid. Berberine sulphate crystallises out, and is decomposed by freshly-precipi-

[1] A concentrated liquid extract of barberry root still receives a limited application for dyeing silk and leather yellow. In America, the root-bark is commonly used, but in Europe the entire root is generally employed.

tated hydroxide of lead. The alkaloid may also be converted into the sparingly soluble nitrate or hydrochloride instead of the sulphate.

L. Wolff recommends a previous treatment of the root with petroleum ether to remove fixed oil.

Berberine may be isolated from barberry or calumba root by exhausting the material with alcohol, evaporating off the spirit, taking up the residue with water, and treating the filtered solution with excess of hydrochloric acid, when berberine hydrochloride crystallises out. The salt may be purified by re-solution in alcohol and precipitation by ether.[1]

Berberine crystallises with difficulty in small, concentrically grouped prisms, or bright yellow, silky needles.[2] When air-dried, the crystals appear to contain 5½ aqua (W. H. Perkin, jun.), of which 3 aqua is driven off at 100°. At this temperature the crystals lose their lustre and become yellowish-brown, at 110° the change is very rapid, and above 160° total decomposition occurs. Fleitmann gives 120° as the melting-point of berberine, but Perkin considers this figure too low.[3]

When warmed, berberine emits a faint but peculiar odour resembling quinone.

Berberine has a persistent, very bitter taste, and is employed medicinally in doses of 2 to 5 grains. Sixty grains have been taken by man without injury, but the alkaloid is poisonous to dogs and other of the lower animals.

Berberine dissolves in 500 parts of cold water, and more readily on boiling. The solution is neutral to litmus. It is sparingly soluble in cold, but readily in hot alcohol, and in amylic alcohol. Berberine is slightly soluble in chloroform and benzene, and insoluble in ether (separation from oxyacanthine and hydrastine) and petroleum spirit. It is said to be taken up with difficulty

[1] Berberine may also be prepared by precipitating an aqueous decoction of barberry root with lead acetate, and treating the concentrated filtrate with excess of sulphuric acid. The precipitate of berberine sulphate is washed with cold water, and separated from lead sulphate by solution in boiling water, which on cooling deposits the salt in yellow needles.

[2] An orange colour, or other shade darker than bright yellow, is indicative of impurity.

[3] E. Schmidt has obtained some evidence that berberine prepared from the commercial sulphate is occasionally a mixture of berberine with methyl-berberine. He obtained pure berberine by converting the alkaloid into the acetone compound, B,C_3H_6O, from which the free base was liberated by heating in alcoholic solution. Thus obtained, berberine contained 6 aqua, all of which was lost at 100° C. The anhydrous alkaloid scarcely began to darken below 150°.

from its acidulated solutions by amylic alcohol, chloroform, and benzene.[1]

When treated with a fixed caustic alkali, berberine is coloured brown, and on boiling a resinous mass separates. On distilling berberine with milk of lime, quinoline is formed. Fusion with caustic potash produces berberic acid, $C_8H_8O_4$, and an acid of the composition $C_8H_8O_5$.

When boiled with excess of fuming hydriodic acid, two methyl groups are eliminated and a salt of berberoline, $C_{18}H_{11}(OH)_2NO_2$, formed. On rendering the diluted liquid slightly alkaline by ammonia, an intense blackish-blue coloration is obtained, probably owing to oxidation. Nitric acid gives, with berberoline, a magnificent violet coloration, which on standing or warming changes to a deep reddish-brown.

Concentrated nitric acid dissolves berberine to a dark, reddish-brown liquid, which on dilution with water gives a yellow flocculent precipitate partly soluble in ammonia. If the dark solution of berberine in strong nitric acid be warmed oxidation rapidly occurs, with formation of berberonic acid (a pyridine-tricarboxylic acid, page 112), oxalic acid, and other products.

Potassium permanganate in presence of potassium carbonate oxidises berberine with formation of hemipinic acid, $C_{10}H_{10}O_6$, and other products (W. H. Perkin, jun., *Jour. Chem. Soc.*, lv. 71).

By the action of nascent hydrogen, berberine is reduced to hydroberberine, $C_{20}H_{21}NO_4$.

Berberine dissolves in concentrated sulphuric acid with orange-yellow colour, changing to olive-green on warming. On adding potassium bichromate, or other oxidising agent, a black colour changing to violet (or brown-violet changing to brownish-yellow) is obtained. Fröhde's reagent gives a brown or green colour with berberine; or, according to Hirschhausen, an immediate yellow, changing through dark brown to violet-brown. Sulpho-vanadic acid is stated to give a fine violet coloration.

[1] According to E. Schmidt (*Pharm. Zeit.*, 1887, page 542), berberine has a remarkable tendency to combine with neutral solvents, such as alcohol, ether, acetone, and chloroform, to form crystalline compounds. When berberine and chloroform are mixed in molecular proportions, they unite to form a beautiful crystalline body, permanent at 100°. This does not appear to be a mere addition-product, since it is not decomposed by acids simply into berberine and chloroform, but yields decomposition-products of the latter. Berberine can also combine with a second molecule of chloroform, but this behaves like water of crystallisation. Schmidt has also described a compound of berberine with acetone, of the formula $C_{20}H_{17}NO_4,C_3H_6O$.

Berberine is also characterised by the insolubility of many of its salts (*e.g.*, the chromate, picrate, hydriodide, chloroplatinate, aurochloride), and the sparing solubility of others in presence of excess of mineral acid.

On pouring chlorine-water (avoiding excess) onto a solution of berberine strongly acidulated with hydrochloric or sulphuric acid, a zone of bright red colour is formed at the junction of the liquids, and is still recognisable as a pink coloration in a dilution of 250,000.[1]

On cautiously adding iodised potassium iodide (avoiding excess) to a solution of a berberine salt, BHI_3 is thrown down as an extremely insoluble red-brown precipitate, which crystallises from strong alcohol in red needles, or on adding water in green iridescent scales which completely polarise light.

Mayer's reagent yields with berberine solutions a precipitate of the approximate composition $B_2H_2HgI_4$, containing, after drying at 100°, from 50 to 52 per cent. of the alkaloid.

SALTS OF BERBERINE.

Berberine is a weak base, but forms definite and readily crystallisable salts with acids. The salts have a bitter taste, and are mostly very sparingly soluble, the pyrophosphate and acetate being exceptions.

Berberine Nitrate, B,HNO_3, separates in fine yellow needles on acidulating a warm aqueous or alcoholic solution of berberine with nitric acid. It is soluble in about 500 parts of cold water, more readily in hot, and almost insoluble in alcohol or water strongly acidulated with nitric acid. It does not darken or undergo other change at 100° C.

Berberine Hydrochloride, $B,HCl+2$ aq, is precipitated in golden yellow needles on adding hydrochloric acid to a warm aqueous solution of the alkaloid. It requires about 500 parts of cold water for solution, and is almost insoluble in alcohol or dilute hydrochloric acid. The salt is with difficulty decomposed by bases, the liberated alkaloid being apt to retain chlorine. Prolonged digestion with litharge fails to decompose it completely, but silver oxide readily decomposes the solution. Berberine hydrochloride darkens to an orange colour when heated to about 60° C., but regains its original colour on cooling. By prolonged exposure at 100° the colour changes permanently, and much of the salt becomes readily soluble in cold water, with red colour.

$BHAuCl_4$ is amorphous, brown, and quite insoluble in water.

[1] Brucine gives a similar reaction with chlorine-water, but the original solution is colourless, and the reaction produced less permanent than with berberine.

It crystallises from boiling dilute alcohol in chestnut brown needles, unchanged at 100°. $B_2H_2PtCl_6$ forms a yellowish precipitate, almost insoluble in all the ordinary solvents. It may be crystallised from boiling amylic alcohol, in which it is slightly soluble.

Berberine Hydriodide, B,HI, obtained by precipitation, forms minute yellow needles, extremely insoluble in cold water or potassium iodide solution. It does not darken or suffer other change at 100°. BHI_3 is precipitated on cautiously adding iodised potassium iodide (carefully avoiding excess) to a solution of a berberine salt in hot spirit. It is quite insoluble in cold water. When recrystallised from hot alcohol, the smaller crystals transmit light which is completely polarised (compare Herepathite, page 403).

Berberine Sulphate, B,H_2SO_4, is met with in commerce both in the amorphous state and crystallised. The latter form, which is considerably the higher priced, can be prepared by dissolving 15 grammes of the amorphous preparation in a boiling mixture of 250 c.c. of alcohol with 8 of acetic acid, when on cooling the crystallised salt separates out. It has an orange colour, and is permanent in the air when free from impurity. It is soluble in about 100 parts of water. According to J. U. Lloyd (*Amer. Drug.*, Sept. 1884), the yellow crystalline powder obtained by heating commercial berberine sulphate with ammonia and shaking with ether is not the free alkaloid, as commonly assumed, but a neutral sulphate, $B_2H_2SO_4$, which is readily soluble in water.

B,H_2CrO_4 is obtained in orange-yellow needles on adding potassium bichromate to a boiling and very dilute solution of a salt of berberine. The salt separates entirely on cooling, and is extremely insoluble in cold water or an excess of the precipitant.

Berberine Picrate requires 45,000 parts of cold water for solution. As a consequence, on mixing aqueous solutions of berberine and picric acid in equivalent proportions and filtering, a liquid is obtained free from yellow colour or bitter taste.

Berberine Acetate is prepared by adding berberine sulphate to a solution of a potassium acetate in rectified spirit, and heating gently till the yellow salt has dissolved. After cooling, the liquid is filtered from the potassium sulphate, evaporated to a syrup, and shaken with ether, when berberine acetate, $B(C_2H_4O_2)_2$, is precipitated as a crystalline orange powder. It is readily soluble in water and alcohol, nearly insoluble in ether, and loses acid on exposure to air.

OXYACANTHINE, $C_{18}H_{19}NO_3$. This base is contained in *Berberis vulgaris*, and remains in the mother-liquor, from which the berberine

has been separated as hydrochloride. The liquid is treated with caustic soda, when a dark-coloured precipitate is thrown down, from which ether dissolves oxyacanthine, berbamine, and an unnamed alkaloid, while another brown-coloured amorphous base remains undissolved. The ethereal solution is treated with acetic acid, and the resultant acetate decomposed by sodium sulphate, when oxyacanthine sulphate is precipitated, berbamine remaining in solution. On decomposing the solution of oxyacanthine sulphate with ammonia the free alkaloid is precipitated in flocks, which, after drying at 100°, melt at 138°–150°; but when crystallised from alcohol or ether it forms anhydrous needles which melt at 208°–214°. Oxyacanthine is readily soluble in chloroform and benzene, but only sparingly in petroleum spirit. It may be separated from berberine by extracting the ammoniacal solution with ether or chloroform. From its acidulated solutions it is not extracted by petroleum spirit or benzene, and only sparingly by chloroform. Oxyacanthine is dextro-rotatory in chloroformic solution (for 4 per cent. at 15°, $S_D = +131{\cdot}6°$). $BHCl + 2H_2O$ forms small colourless needles, the 2 per cent. aqueous solution of which shows $S_D = +163{\cdot}6°$. Hot strong solutions are coloured green by ferric chloride. Oxyacanthine closely resembles narcotine. Like morphine, it reduces iodic acid. Concentrated sulphuric acid, with or without molybdic acid, is stated to give no colour at first, but on standing or heating a yellow colour is developed; according to L. v. Hirschhausen (*Zeit. Anal. Chem.*, xxiv. 163), Fröhde's reagent gives an immediate violet coloration, changing to yellowish green at the edges.

When heated with caustic potash and a little water, oxyacanthine melts to a brown mass which floats on the fused alkali. This consists of the potassium derivative of β-oxyacanthine, a body probably differing from the parent alkaloid by the elements of water. A similar change occurs very readily even at the ordinary temperature, by the action of alcoholic potash or baryta on α-oxyacanthine. Ether fails to extract the β-modification from the alkaline solution. Hydrochloric acid precipitates β-oxyacanthine, which is soluble both in alkalies and excess of acid. With much acid, α-oxyacanthine hydrochloride is precipitated.

Berbamine, $C_{18}H_{19}NO_3$, the second *Berberis* alkaloid soluble in ether, was obtained by Hesse (*Berichte*, xix. 3190) by adding sodium nitrate to the liquid from which oxyacanthine had been thrown down as sulphate. The precipitated berbamine nitrate when decomposed by ammonia yields a crystalline precipitate of the free base, which crystallises from alcohol in small plates con-

taining 2 aq. and melting at 156°. The salts are crystallisable and readily soluble. $B_2H_2PtCl_6$ is yellow, crystalline, and only slightly soluble in water.

Hydrastine. $C_{21}H_{21}NO_6$; or $C_{19}H_{15}(O.CH_3)_2NO_2$ (see also page 470).

This interesting base occurs with berberine (and canadine) in the root of *Hydrastis Canadensis* or Golden Seal.[1] Perrins found 1½ per cent. in the dried root, but the yield in manufacture is from ½ to ¾ per cent. It also occurs in *Stylophorum diphyllum.* Hydrastine differs from berberine in being colourless, but commercial medicinal preparations of berberine from *Hydrastis* are not unfrequently called hydrastine.[2]

Hydrastine forms colourless or milk-white four-sided prisms, melting at 132° and decomposing at a higher temperature with an odour of phenol.

Free hydrastine is tasteless and odourless, but the salts have an acrid taste. The alkaloid is the chief if not the only active principle of *Hydrastis Canadensis.*[2] It is poisonous in large doses, 3 grains being fatal to a frog in four minutes. It resembles strychnine in causing death by arresting the respiratory movements in a tonic spasm.

Hydrastine is insoluble in water, and nearly insoluble in alkaline solutions. It dissolves in 120 parts of alcohol, in 1¾ parts of chloro-

[1] F. Wilhelm extracts the coarsely-powdered root of *Hydrastis Canadensis* with boiling water acidulated with acetic acid, evaporates the decoction to a syrup, and adds excess of dilute sulphuric acid. After standing, the berberine sulphate which crystallises out is filtered off, and the filtrate neutralised with ammonia. The precipitate contains much hydrastine, and on again filtering and adding excess of ammonia to the filtrate a further precipitate is produced, which is said to contain *canadine.* Both precipitates when boiled with ethyl acetate give solutions which on cooling deposit hydrastine in large crystals, which may be purified by crystallisation. The crystals from the second ammonia precipitate are much purer than those from the first. By slow evaporation of the ethyl acetate solution the hydrastine is obtained in prisms as large as walnuts.

Eberhardt purifies hydrastine by dissolving the freshly-precipitated alkaloid in a minimum of boiling chloroform, filtering through glass-wool, and pouring the solution into excess of cold alcohol. On shaking the liquid vigorously for some minutes, the hydrastine separates as a fine crystalline precipitate, which is subjected to a repetition of the process and recrystallised from boiling alcohol.

[2] The root of Golden Seal is a bitter tonic analogous to calumba. It is exhibited in the form of powder and in doses of 8 to 24 grains. The hydrochlorides of the mixed alkaloids of golden seal are sometimes sold under the name of "hydrastine."

form, in 16 of benzene, and in 83 of ether. It is quite insoluble in petroleum spirit. The solubility of hydrastine in ether may be utilised to separate it from berberine. Hydrastine is lævo-rotatory, S_D in chloroformic solution (1·2759 gramme in 50 c.c.) being −67·8°.[1]

Hydrastine is a feeble base, and is completely extracted by chloroform from solutions freely acidulated with hydrochloric acid. In part, however, it is dissolved as hydrochloride, which salt is very soluble in chloroform.

With the exception of the picrate, the salts of hydrastine are generally uncrystallisable, or are obtainable in crystals by special means only. Most of them, except the tannate and picrate, are soluble in water, the solutions having an acid reaction.

Hydrastine hydrochloride and sulphate are used in medicine.[2] B,HCl is best prepared by passing dry hydrochloric acid gas over the surface of a solution of hydrastine in anhydrous and alcohol-free ether. After drying over sulphuric acid the precipitate forms a micro-crystalline powder easily soluble in water and chloroform. B,H_2SO_4 is similarly obtained by cautiously adding a solution of strong sulphuric acid in ether to an ethereal solution of hydrastine. The salt readily takes up water and forms a gummy mass.

Hydrastine solutions give no colour-reaction with chlorine-water. With iodised potassium iodide they yield a deep brown flocculent precipitate.

Hydrastine may be approximately determined by titration with Mayer's reagent (page 141), but the precipitating power of the solution is materially affected by the dilution of the liquid.

Picric acid forms in hydrastine solutions a yellow amorphous precipitate of the picrate, $B\bar{A}+4$ aq, which is deposited in splendid yellow needles from its solution in boiling alcohol.

Solutions of hydrastine are precipitated by potassium bichromate. On touching the separated precipitate with a drop of strong sulphuric acid, it *instantly* becomes bright red, the colour fading in a few seconds. This behaviour distinguishes hydrastine from strychnine and gelsemine (page 368).

If a solution of hydrastine be acidulated with sulphuric acid, and a few drops of a decinormal solution of potassium permanganate added, the colour of the reagent is instantly discharged, and an intense blue fluorescence is developed. A single drop of a 1 per

[1] The figure for specific rotation given in the text is that of Freund and Will. Eijkman practically confirms this. F. B. Power (*Pharm. Jour.*, [3], xv. 298) gives the widely different figure −170°.

[2] The *crystallised* sulphate of hydrastine advertised by some manufacturers is simply sulphate of berberine, to which the name hydrastine is persistently misapplied.

cent. solution of hydrastine when treated in this way renders a large test-tube of liquid strongly fluorescent (A. B. Lyons, *Pharm. Jour.*, [3], xvi. 880). Excess of permanganate must be avoided, or both the alkaloid and fluorescent product will be destroyed. The fluorescent body differs from æsculin in not being extracted from either acid or alkaline solutions by chloroform or ether, and in not having the fluorescence intensified by addition of alkali.[1]

The colour-reactions of solid hydrastine have been re-investigated by A. B. Lyons (*Pharm. Jour.*, [3], xvi. 880) with the following results:—Concentrated sulphuric acid dissolves the pure alkaloid with faint yellow colour, changing to a deep blue-purple on heating. If the reagent contains a trace of nitric acid a yellow colour is produced, and with a larger proportion (1:1000) the colour is orange-red. Pure nitric acid produces a permanent orange solution, which on adding water deposits an insoluble substance, and yields a liquid exhibiting an intense blue fluorescence (compare last page).

With sulphuric acid and oxidising agents (compare page 368) hydrastine produces some well-defined colour-reactions. With manganese dioxide an orange colour is first developed, changing to a rich cherry-red, and passing through carmine to a yellowish shade of red, which after a time changes rather suddenly to a pale orange-yellow. This reaction distinguishes hydrastine from strychnine and gelsemine, while berberine dissolves in sulphuric acid with yellow colour, changing on addition of the oxidising agent to violet, then to chocolate-brown, and finally becoming orange-red. (The intermediate chocolate-brown stage distinguishes the berberine reaction from that given by strychnine.) Potassium permanganate gives with hydrastine and sulphuric acid the same colorations as manganese dioxide, but the changes are more rapid. A violet tint is sometimes produced *after* the red is developed, the contrary order being characteristic of strychnine.

Fröhde's reagent gives with hydrastine a sage-green colour, slowly changing to brownish, and then gradually fading. This succession of tints is very characteristic. Sulphovanadic acid gives a rose-red colour, which fades slowly.

On treating an acid solution of hydrastine with oxidising agents (*e.g.*, manganese dioxide and sulphuric acid), it splits up into opianic acid (page 298) and hydrastinine, a base closely resembling cotarnine (page 299). If the oxidation be effected in

[1] The same fluorescent oxidation-product is sometimes developed in solutions of hydrastine by mere exposure to air. Neither pure hydrastine nor any ready-formed constituent of *Hydrastis* root appears to be fluorescent.

alkaline solution, the action proceeds further, the chief products being hemipinic (page 299) and nicotinic acids (page 111). This behaviour suggests a close relationship between hydrastine and narcotine, but hitherto all attempts to convert one of these bases into the other have been unsuccessful.[1]

HYDRASTININE, $C_{11}H_{11}NO_2 + H_2O$, produced together with opianic acid by the action of oxidising agents on hydrastine, forms white crystals, melting at 116°–117° C., or at 100° after heating for some time to that temperature. It dissolves in water to form a strongly alkaline and very bitter solution. It is also soluble in ether, ethyl acetate, benzene, and petroleum spirit, and crystallises from each of these solvents with 1 aqua, which, however, is eliminated in the salts, a fact probably due to the formation of a closed ring. $C_{11}H_{11}NO_2,HCl$ crystallises in feebly coloured needles, soluble in water and alcohol. The aqueous solution is optically inactive and feebly fluorescent. B,H_2SO_4 forms yellow crystals showing a green fluorescence, and is soluble in alcohol. Hydrastinine, when treated with aqueous potash, yields hydrohydrastinine, $C_{11}H_{13}NO_2$, and oxyhydrastinine, $C_{11}H_{11}NO_3$. The latter is a feeble base, melting at 97°–98° and distilling above 350°, and forms crystallisable salts. The former base is also formed by the action of reducing agents on hydrastinine. It forms white crystals melting at 66°, and yields crystallisable salts.

When hydrastinine is oxidised in dilute alkaline solution with a cold saturated solution of potassium permanganate, it is converted almost quantitatively into oxyhydrastinine, $C_{11}H_{11}NO_3$. Excess of the oxidising agent and slight heating carries the oxidation to hydrastinic acid, $C_{11}H_9NO_6$, a body crystallising in flat needles melting at 164°, soluble in alcohol and ether, and yielding no precipitate with silver, barium or lead salts.[2]

CANADINE, $C_{21}H_{21}NO_4$, is an alkaloid accompanying berberine and hydrastine in golden seal root. Until recently there was some doubt as to its actual existence, Lloyd having failed to detect it in the extract from a very large quantity of the root; but F.

[1] E. Schmidt considers that narcotine contains three methoxyl groups and hydrastine only two, their formulæ being respectively $C_{19}H_{14}(OMe)_3NO_4$ and $C_{19}H_{15}(OMe)_2NO_4$. As these bases both yield on oxidation opianic acid, which contains two methoxyl groups, and cotarnine contains one such group, it follows that hydrastine contains no methoxyl, and that cotarnine has the constitution of a methylated hydrastinine.

[2] The constitution of hydrastinine and hydrastine has been the subject of various investigations by Freund, Will, Rose, Rosenberg, Lachman, Schmidt, Wilhelm, Kerstein, Heim, Philips, Dormeyer, and others (*Berichte*, xix. 2797;

Wilhelm and E. Schmidt have independently isolated the alkaloid, which is described as forming fine, white, shining crystals, *melting at* 134°, and more readily soluble than berberine in water and alkalies.

The salts, with the exception of the sulphate, are soluble with difficulty in water and alcohol. B,HCl and B_2,H_2SO_4 are crystalline. By treatment with iodine in alcoholic solution, canadine is converted into the hydriodide of methyl-berberine, and hence it probably has the constitution of a dihydromethylene-berberine.

XANTHOPUCCINE is the name proposed by Lerchen (1878) for an alkaloid of doubtful existence occurring in hydrastis. It is described as insoluble in ether and chloroform, but soluble in alcohol and hot water. The alcoholic solution yields light brown spangles with iodised potassium iodide.

Indications of other alkaloids in hydrastis have been obtained by A. K. Hale (*Year-Book Pharm.*, 1874, page 31) and J. C. Burt (*ibid.*, 1886, page 95).

Calumba, or COLUMBA,[1] is the root of *Jateorhiza Calumba* or *Cocculus palmatus*, a herbaceous climbing plant occurring in the forests of East Africa.

The calumba of commerce consists of dried transverse slices of the root. It possesses mild bitter tonic properties, and the tincture, extract, and infusion are official preparations. The roots of bryonia and *Frasera Walteri* have been occasionally sold as calumba.

Calumba root contains three distinct bitter principles in addition to starch (35 per cent.), gum (4·7), pectin (17), resin, wax, and

xx. 80, 2400; xxii. 456, 1156, 2322, 2329; xxiii. 404, 416, 2469, 2897, 2920; xxiv. 2730, 3164; *Arch. Pharm.*, [3], xxvi. 329; xxviii. 49, 221).

M. Freund (*Ber.*, xxii. 2329) suggests the following structural formulæ for hydrastinine and its derivatives:—

Hydrohydrastinine, . . . $CH_2\left\{\begin{matrix}O\\O\end{matrix}\right\}C_6H_2\left\{\begin{matrix}CH_2.NMe\\CH_2.CH_2\end{matrix}\right\}$

Hydrastinine, ... $CH_2\left\{\begin{matrix}O\\O\end{matrix}\right\}C_6H_2\left\{\begin{matrix}COH.NHMe\\CH_2.CH_2\end{matrix}\right\}$

Oxyhydrastinine, . . . $CH_2\left\{\begin{matrix}O\\O\end{matrix}\right\}C_6H_2\left\{\begin{matrix}CO.NMe\\CH_2.CH_2\end{matrix}\right\}$

For hydrastine itself Freund suggests the following formula:—

$$CH_2\left\{\begin{matrix}O\\O\end{matrix}\right\}C_6H_2(CH_2.CH_2.NHMe).C⋮C.C_6H_2(OMe)_2.COOH.$$

On decomposition into hydrastinine and opianic acid, fission would take place at the point of triple linkage, both the acid and the basic derivative possessing aldehydic functions.

[1] German; *Kalumba or Columbo wurzel.* French; *Racine de Columbo.*

mineral matter (6 per cent.). Potassium nitrate has been found, but not tannin. Berberine, the characteristic yellow alkaloid of calumba root has already been described (page 462).

Columbin, or Calumba Bitter, $C_{21}H_{22}O_7$, exists in calumba root to the extent of 0·34 to 0·40 per cent. To extract it, the material is exhausted with boiling alcohol, the extract evaporated to dryness, the residue taken up with hot water, and the filtered liquid shaken with ether; or the tincture is evaporated to a syrup, and shaken with chloroform. The chloroform solution is filtered, evaporated, and treated with 60 per cent. alcohol, which dissolves most of the colouring matter. The residue is dissolved in strong alcohol, the solution decolorised with animal charcoal, and the columbin crystallised. Columbin is an intensely bitter, inodorous, neutral body. It melts at 182°, and crystallises from acetic acid solution in colourless trimetric prisms, very slightly soluble in cold water, more freely in hot.

Columbin is sparingly soluble in cold alcohol, and in 40 parts of the boiling solvent. It dissolves with difficulty in cold ether, more readily in hot, and may be separated from berberine by agitating the acidulated liquid with this solvent.

The solution of columbin is intensely bitter; it is not precipitated by tannin or any metallic salts.

Columbin dissolves in strong sulphuric acid with orange colour, changing to deep red; on adding water brown flakes are deposited. Columbin dissolves in aqueous alkalies, and is reprecipitated by acids. On heating with caustic alkali an acid body is formed. According to Houdé, columbin produces vomiting and diarrhœa. 0·10 gramme was fatal to a fowl, death being preceded by digestive disturbance and frequent evacuations (*Pharm. Jour.*, [3], xvi. 838).

Columbic Acid, $C_{22}H_{24}O_5+H_2O$, is prepared by treating the dried alcoholic extract of calumba root with lime-water, and precipitating the solution with hydrochloric acid. It is a yellow amorphous body, somewhat less bitter than columbin; nearly insoluble in water, but little soluble in ether, more readily in acetic acid, and easily in alcohol. The alcoholic solution precipitates lead acetate yellow.

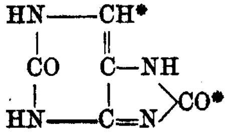
CAFFEINE AND ITS ALLIES.

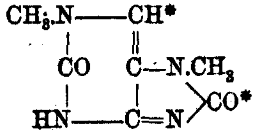
Caffeine, the characteristic alkaloid of *coffee*, was obtained pure in 1821, when it was prepared almost simultaneously by Runge, Pelletier and Caventou, and Robiquet. In 1827, Oudry

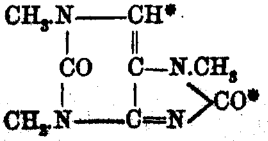
discovered a similar principle in *tea*, and named it theine. Berzelius suggested the identity of this with caffeine, and this was afterwards established, as also was that of the alkaloid of *guarana*, called by Martius guaranine. *Maté*, or Paraguay tea, and *Kola nuts* contain the same alkaloid, while *cocoa* contains the alkaloid theobromine (which may be regarded as a lower homologue of caffeine) in addition to small quantities of caffeine.

Unlike the majority of the alkaloids hitherto described, theobromine and caffeine are not related to pyridine or quinoline. They are respectively the di- and tri-methyl-derivatives of xanthine, $C_5H_4N_4O_2$, a weak base forming the chief constituent of certain rarely-found urinary calculi, and existing constantly to a minute extent in normal urine and in most of the organs of the human body. Xanthine itself is closely allied to uric acid, $C_5H_4N_4O_3$, from which it differs by a single atom of oxygen, and from which it can be produced by treatment with sodium amalgam and water. On adding silver nitrate to an ammoniacal solution of xanthine, an amorphous precipitate of the silver-derivative, $C_5H_2Ag_2N_4O_2$, is formed, and this when heated with methyl iodide is converted into dimethyl-xanthine or theobromine, $C_5H_2(CH_3)_2N_4O_2$. When the silver-derivative of theobromine, $C_5HAg(CH_3)_2N_4O_2$, is heated with methyl iodide to 160° C. for twenty hours, trimethyl-xanthine or caffeine, $C_5H(CH_3)_3N_4O_2$, is produced.

The following formulæ show the constitution of caffeine and theobromine, and their relation to xanthine :[1]—

Xanthine, . . 

Theobromine, . . 

Caffeine, . . 

[1] The formulæ given in the text are those proposed by Emil Fischer (*Annalen*, ccxv. 314). In the formulæ of Medicus (*Annalen*, clxxv. 250), the CH and CO groups marked with an asterisk are transposed.

Theophylline (see page 498), a base isomeric with theobromine, has been found in minute quantity in tea, as also has xanthine itself.[1]

Caffeine.[2] Theine.[2] Trimethyl-xanthine. Methyl-theobromine.

$$C_8H_{10}N_4O_2 \text{ ; or } C_5H(CH_3)_3N_4O_2 .$$

The constitution and synthesis of caffeine have already been described (see page 473).

Caffeine exists naturally in the following sources, all of which are employed for food or preparing beverages:—

a. Coffee;[2] the dried seed of *Coffea Arabica.*

b. Tea;[2] the prepared and dried leaves of *Camellia Thea.*

c. Maté or Paraguay tea; the dried leaves and twigs of *Ilex Paraguayensis.*

d. Guarana or Brazilian chocolate; the dried pulp of the seed of *Paullinia sorbilis.*

e. Cola; the seeds or nuts of the Kola tree (*Cola* or *Sterculia acuminata*) of West Central Africa.

Caffeine is found in other parts of these plants besides those commonly used for food, and also occurs in small quantity, together with theobromine, in cocoa.

Caffeine can be isolated with facility in a state of considerable purity, but its quantitative determination is attended with considerable uncertainty, chiefly owing to the difficulty of completely extracting it from its natural sources (see page 488).

Caffeine is now prepared on a considerable scale from damaged tea.[3] Several methods have been employed for the purpose, one of the simplest being to exhaust the tea with boiling water, boil

[1] For the isolation of xanthine from tea, A. Baginsky extracted the material with dilute sulphuric acid, treated the clear liquid with baryta-water in excess, and then passed carbon dioxide to precipitate the excess of baryta. After filtering and evaporating, ammonia and silver nitrate were added, and the resultant precipitate of xanthine-silver crystallised from its solution in dilute nitric acid to which some urea had been added. The xanthine-silver nitrate obtained contained 33·6 per cent. of Ag, or very nearly the amount required by the formula $C_5H_4N_4O_2,AgNO_3$. The weight obtained from 1 lb. of tea was only 0·1567 gramme (*Pharm. Jour.*, [3], xix. 41).

[2] The absolute identity of the alkaloids of tea and coffee is generally accepted, but cannot be said to have been established absolutely beyond doubt. According to Lauder Brunton and Cash (*Proc. Royal Society*, 1887), the physiological effects of the alkaloids extracted from tea and coffee exhibited marked differences. Theine (from tea) appeared to be more powerful in its action than caffeine (from coffee), and tended to produce rhythmical contractions of the voluntary muscles. These observations have not been confirmed.

[3] A few years since the manufacture of caffeine was almost monopolised by Germany. In consequence of a revised regulation of the English customs,

the decoction with litharge or acetate of lead, and concentrate the filtered solution till the alkaloid crystallises out on cooling. The product can be purified by resublimation, or by crystallisation from hot water.

Caffeine forms long, white, silky, flexible needles, which readily felt together to form light fleecy masses. When deposited slowly from an aqueous or chloroformic solution, the crystals of caffeine present a characteristic appearance under a magnifying power of 100 to 300 diameters.

It is generally stated that caffeine crystallises from water with 1 aqua (8·49 per cent.), but the proportion ordinarily present in crystallised caffeine is sensibly less than corresponds to this formula. Thus Pfaff and Liebig found 7·85 and Martius 8·14 per cent., and the author in two commercial specimens obtained 7·05 and 7·10 per cent.[1] It is probable that the deficiency is due to efflorescence, for the water of crystallisation is lost by prolonged exposure over concentrated sulphuric acid at the ordinary temperature and pressure, so that the caffeine so treated suffers no further loss of weight at 100°.

On heating crystallised caffeine to 100° C. the crystals become opaque and friable, consequent on the loss of water, the residue consisting of anhydrous caffeine and dissolving without turbidity in chloroform. According to Mulder, caffeine is deposited in anhydrous crystals from alcohol or ether, and under certain conditions from water also. It is possible that hydration may depend on unrecognised conditions, such as those of temperature and concentration of the solution at the time of separation, and that commercial caffeine is a variable mixture of anhydrous and hydrated crystals.

Caffeine does not evaporate with vapour of water, and undergoes no appreciable change of weight at 100° (A. H. Allen).[2] At 120° it volatilises very gradually, and at a higher temperature sublimes unchanged in long, silky needles.

according to which damaged tea is admitted duty-free, provided that it be "denatured" and rendered wholly unfit for human consumption by treatment with lime and assafœtida, it has become possible to use such tea profitably for the manufacture of caffeine. As a result, England has become the chief seat of the manufacture, and now exports the alkaloid to Germany and America. At present (August, 1892) the retail price of caffeine from tea is 9d. per ounce.

[1] Mulder found 8·49 per cent. of water, but that was by exposing the substance to a temperature above 120°, when more or less volatilisation must have taken place.

[2] The statements respecting the effect of heat on caffeine are very discordant. According to A. Wynter Blyth, caffeine sublimes in minute needles at

At 231°–233° C. caffeine melts to a clear liquid, and at 384° (Strecker) boils and distils with partial decomposition, leaving no résiduum.

79° C., and volatilises completely at 120°. Other observers give much higher temperatures for its subliming point.

The behaviour of caffeine when heated has an important bearing on the methods of determining the alkaloid, and hence has recently been carefully re-investigated in the author's laboratory by G. E. Scott Smith, C. M. Caines, and G. S. A. Caines. The following facts have been fully established :—

1. Commercial caffeine (crystallised) lost 6·9 per cent. of its weight by prolonged drying over concentrated sulphuric acid at the ordinary temperature and pressure.

2. Caffeine which has been dried at the ordinary temperature over sulphuric acid till constant in weight undergoes no further material loss on prolonged exposure in an open dish in the water-oven at 100°. The following results were obtained :—

	Caffeine.	Loss.
Weight of commercial alkaloid taken, . .	1·000 gramme.	...
,, after long exposure over H_2SO_4 at 20° C.,	0·931 ,,	6·9 per cent.
,, after heating in water-oven for 2½ hours,	0·929 ,,	7·1 ,,
,, ,, ,, 6½ ,,	0·929 ,,	7·1 ,,
,, ,, ,, 51 ,,	0·927 ,,	7·3 ,,

3. Notwithstanding the foregoing results, on heating caffeine contained in a watch-glass, covered with another watch-glass, over boiling water or on the top of the water-oven for fifteen minutes, a distinct film appeared on the covering glass, and crystals of caffeine were observable under the microscope. The slight loss of weight observed when caffeine was exposed for many hours at 100° is doubtless due to volatilisation.

4. On exposing dry caffeine to a temperature of 120° in an air-bath, a very gradual but continual decrease of weight was observed, indicating sensible volatilisation of the alkaloid at the temperature employed. Thus :—

	Weight of Alkaloid.	Loss.	
	Grammes.	Grammes.	Per cent.
Moisture-free caffeine taken, .	0·9290	...	...
After heating for 2 hours at 120°,	0·9260	0·0030	0·32
,, ,, 6 ,, ,,	0·9270	0·0220	2·37
,, ,, 11 ,, ,,	0·8668	0·0622	6·69
,, ,, 14 ,, ,,	0·8314	0·0976	10·50
,, ,, 17 ,, ,,	0·7850	0·1440	15·50
,, ,, 20 ,, ,,	0·7654	0·1536	16·53
,, ,, 24 ,, ,,	0·7568	0·1722	18·53
,, ,, 29 ,, ,,	0·7486	0·1804	19·42

Caffeine is odourless, but has a bitter taste. It has a marked physiological action, and in excessive doses possesses decided poisonous properties. Administered to frogs, it produces tetanus and rigor of the voluntary muscles. A cat was killed in thirty-five minutes by administering ¼ gramme of alkaloid. In all experiments with caffeine on the lower animals there has been increased frequency of the heart's action, and repeated emptying of the bladder and intestines. After death, the alkaloid has been detected in the blood, the bile, and the urine. In man, caffeine increases the heart's action, by stimulating the cardiac muscles, and excites the nervous system.

The *British Pharmacopœia* gives from 1 to 5 grains as the medicinal dose of caffeine; the *German Pharmacopœia* states the maximum single dose at 0·2 gramme, and the daily maximum dose at 0·6 gramme.

The physiological action of infusions of tea and coffee is in part due to the caffeine, but is largely modified by the other constituents; notably the tannin, extractive matter, and possibly the essential oil of tea, and the caffeol or essential oil of coffee.

Caffeine is only sparingly soluble in cold water (75 to 80 parts), but tolerably readily in hot (10 parts). It dissolves in about 35 parts of cold rectified spirit, but it is much less soluble (1 : 155) in absolute alcohol. In cold ether it is very sparingly soluble, more readily in amylic alcohol, chloroform and benzene, but nearly

5. Caffeine which had been recently sublimed and was consequently anhydrous, melted at 231·5° C., and resolidified at 223° C. Strecker gives the melting-point of anhydrous caffeine as 234°, and Biedermann at 230·5°. Mulder gives the melting-point at 177·8°, which is certainly too low.

6. Caffeine which had been recently sublimed and then dissolved in water, alcohol, ether or chloroform, in each case left the original weight of alkaloid on evaporating the solution and exposing the residue at 100°. The same result was obtained with recently-fused caffeine. As sublimed and fused caffeine are certainly anhydrous, it follows that the alkaloid left on evaporating its solutions in the above solvents is also anhydrous.

7. When a known weight of caffeine was repeatedly treated with a small quantity of water, and the liquid evaporated to dryness at 100°, the original weight was always recovered. When caffeine, previously dried at 100° or 120°, or recently sublimed or fused, was dissolved in 1000 parts of distilled water, the solution concentrated by boiling over a naked flame, and the evaporation completed in a platinum dish at 100°, the residue being finally dried in the water-oven, the weight of alkaloid originally taken was strictly recovered. This proves that caffeine does not volatilise with steam during the evaporation of its solutions (A. H. Allen, *Pharm. Jour.*, [3], xxiii. 213).

insoluble in carbon disulphide and petroleum spirit.[1] Chloroform and benzene dissolve out the alkaloid even from its acidulated aqueous solutions, but the agitations must be several times repeated to effect complete extraction.

Concentrated sulphuric acid converts caffeine into the sulphate, but does not colour or otherwise change it even at 100° C.[2]

Hydrochloric acid has no action on caffeine below 200°, but when heated under pressure with concentrated hydrochloric acid to 250° for six to twelve hours caffeine yields ammonia, methylamine, sarcosine, carbon dioxide, and traces of formic acid. The volume of methylamine produced is double that of the ammonia, which proves the presence of three NMe groups in caffeine, and establishes the following formula for the reaction:—$C_8H_{10}N_4O_2 + 6H_2O = NH_3 + 2N(CH_3)H_2 + C_3H_7NO_2 + CH_2O_2 + CO_2$ (E. Schmidt, *Annalen*, ccxvii. 270).[3]

When caffeine is warmed with dilute caustic alkali or boiled with concentrated baryta-water, it at first assimilates the elements of

[1] A. Commaille (*Compt. Rend.*, cxxxi. 817; *Jour. Chem. Soc.* xxix. 779) gives the following figures for the solubility of hydrated and anhydrous caffeine in different menstrua:—

Solvent.	Parts of Solvent required for 1 of Caffeine.		
	At 15° to 17° C.		At Boiling-point of Solvent.*
	Hydrated.	Anhydrous.	Anhydrous.
Water,	68	74	2·2
Rectified spirit,	40	44	...
Absolute alcohol,	...	165	82
Commercial ether,	476	526	...
Pure anhydrous ether,	...	2288	277
Chloroform,	...	7·7	5¼
Carbon disulphide,	...	1709	220
Petroleum ether,	...	4000	...

* The hot water was at 65° only, not at the boiling-point.

[2] Experiments by the author showed that pure caffeine was wholly unchanged when heated in the water-oven for several hours with concentrated sulphuric acid. On dissolving the product in water, boiling with oxide of lead, filtering, concentrating, and extracting with chloroform, the original weight of caffeine was recovered. Some samples of commercial caffeine darken slightly when heated with sulphuric acid.

[3] Schmidt thought it possible that theobromine might be formed in this reaction by the elimination of a methyl-group, but was not able to detect it. The methylamine was separated and purified by conversion into the chloroplatinate. The sarcosine was identified by means of its copper salt.

water and is converted into an acid containing $C_8H_{12}N_4O_3$.[1] On further treatment, this body splits up with great facility into carbon dioxide and the base caffeidine, $C_7H_{12}N_4O$.[2] On still further boiling with the alkali this is again decomposed with formation of carbon dioxide, formic acid, ammonia, methylamine, and sarcosine (methyl-amidoacetic acid).

The author has proved that caffeine readily undergoes decomposition when boiled with lime-water, a fact which has a practical bearing on several of the published processes for its determination. When caffeine is boiled with magnesia and water, the decomposition is insignificant, and with litharge there is no change.

[1] CAFFEIDINE-CARBOXYLIC ACID, $C_8H_{12}N_4O_3$, or $C_7H_{11}N_4O.COOH$, is best prepared by digesting finely-divided caffeine for some hours at 30° C. in a dilute solution of caustic potash or soda, neutralising with acetic acid, adding cupric acetate (avoiding excess), and decomposing the resultant precipitate by sulphuretted hydrogen. The liberated acid obtained on evaporation of the filtrate *in vacuo* at the ordinary temperature, may be purified by solution in chloroform and precipitation with benzene, and is thus obtained in the form of a thick oil, which on exposure to the air solidifies to a yellowish-white, slightly crystalline mass, very soluble in water to a strongly acid liquid. It is soluble in alcohol and chloroform, but insoluble in benzene. On boiling the aqueous solution of caffeidine-carboxylic acid, carbon dioxide is evolved and a reddish oil remains, which when stirred up with a small quantity of sulphuric acid and treated with alcohol solidifies to a white crystalline mass of *caffeidine sulphate*. The reaction affords a ready method of preparing caffeidine. It is merely necessary to decompose the copper salt with sulphuretted hydrogen, evaporate the filtrate rapidly, and treat it with strong sulphuric acid. The *copper salt* of caffeidine-carboxylic acid, $Cu(C_{16}H_{11}N_4O_3)_2$, is a pale blue crystalline powder, nearly insoluble in water and wholly so in alcohol. The barium, calcium, zinc, cadmium, and magnesium salts are nearly insoluble in water, but the *lead* salt is soluble. $K\bar{A}$ is a yellow oil. On adding mercuric chloride to the solution of a soluble caffeidine-carboxylate, a copious white precipitate is obtained which appears to contain $(C_8H_{11}N_4O_3)_2Hg,2HgCl_2$. If this be suspended in water and decomposed with sulphuretted hydrogen, the filtered liquid leaves caffeidine hydrochloride on evaporation.

[2] CAFFEIDINE, $C_7H_{12}N_4O$, may be obtained as above described, or may be prepared by boiling caffeine with a solution of 10 parts of crystallised baryta for half an hour, or until ammonia and methylamine begin to be evolved. From the product of the reaction, *caffeidine sulphate*, BH_2SO_4, is obtained by acidulating the filtered liquid with dilute sulphuric acid, and evaporating the filtrate to a thin syrup, when the salt is deposited in readily soluble needles. The free base is an oily, strongly alkaline liquid, readily soluble in water, alcohol and chloroform, but with difficulty in ether. It reduces silver oxide, even in the cold, and decomposes very readily into ammonia, methylamine, and cholestrophane (dimethylparabanic acid), $C_3H_2Me_2N_2O_3$. Caffeidine nitrate, hydrobromide, and hydrochloride crystallise well. $B_2H_2PtCl_6$ crystallises from water in large orange-yellow needles, containing either 2 or 4 aqua.

When caffeine is heated with soda-lime to 180°, ammonia is evolved, and carbonate and a large quantity of cyanide formed. According to Rochleder this last product distinguishes caffeine from piperine, morphine, quinine, and cinchonine. When caffeine is ignited with excess of soda-lime, the nitrogen is evolved as ammonia, any cyanide formed as an intermediate product at a lower temperature being decomposed in the usual manner; but in order to ensure complete conversion of the nitrogen into ammonia, it is better to mix the caffeine with about twice its weight of cane-sugar (A. H. Allen).

When caffeine is treated with bromine-water, avoiding excess, and the liquid evaporated to dryness at 100°, a yellowish residue is left, which becomes crimson-red on further heating, and is turned a magnificent purple by ammonia. The reaction is very delicate, and is not affected by a considerable excess of ammonia. On adding caustic soda complete and instant decolorisation occurs.

Another modification of the test consists in treating a minute quantity of the solid substance (such as a residue of caffeine left on evaporation) in a porcelain dish with a few drops of strong hydrochloric acid and a minute crystal of potassium chlorate, and evaporating the liquid to dryness at 100°. When cold, the reddish-yellow or pinkish residue is cautiously moistened with ammonia, avoiding an excess, when the characteristic purple coloration is produced; or, preferably, it is exposed to ammoniacal vapours by inverting the dish bearing the residue over another containing strong ammonia.

The products of the oxidation of caffeine include amalic acid,[1] which by subsequent treatment with ammonia is converted into murexoïn; the reactions being identical to the eye and parallel in chemical change to those yielded by uric acid under like conditions. Thus:—

	Uric acid yields	Caffeine yields
With the oxidising agent, .	Alloxantin. $C_8H_6N_4O_8$	Amalic acid. $C_8H_2(CH_3)_4N_4O_8$
On adding ammonia, . . .	Murexide. $NH_4.C_8H_4N_5O_6$	Murexoïn. $NH_4.C_8(CH_3)_4N_5O_6$

Strong nitric acid may be substituted for the bromine-water or hydrochloric acid and potassium chlorate; but the reaction is in that case far less distinct and easy to regulate, and excess of ammonia must be carefully avoided.[2]

[1] AMALIC ACID forms colourless crystals which stain the skin red, and are very sparingly soluble in water or alcohol. It reduces silver salts, and forms deep violet compounds with potash, soda, and baryta.

[2] O. Hehner, in a private communication to the author, points out that, if the nitric acid used be perfectly pure, caffeine fails to give the murexoïn reaction, but that in presence of a minute trace of hydrochloric acid the colour is readily developed.

Theobromine and xanthine give similar reactions to caffeine with an oxidising agent and ammonia. The purple colorations due to caffeine and theobromine are decolorised by adding caustic alkali solution, but that due to uric acid is changed to blue.

When caffeine is heated with a large excess of nitric acid, it is converted into cholestrophane[1] or dimethylparabanic acid, $C_3(CH_3)_2N_2O_3$, a body which crystallises in pearly laminæ, melting at 145·5°, boiling at 275°–277°, and difficultly soluble in cold water and alcohol. It is decomposed with great facility by alkalies into symmetrical dimethylurea (melting at 97°–100°) and oxalic acid. Hence on adding ammonia and calcium chloride to its aqueous solution, and warming the liquid, calcium oxalate is precipitated.

Cholestrophane is also produced (35·4 to 41·8 per cent.) by oxidising caffeine with chromic acid mixture, the main reaction being:—

$$C_5H(CH_3)_3N_4O_2 + O_3 + 2H_2O = C_3(CH_3)_2N_2O_3 + NH_2(CH_3) + NH_3 + 2CO_2.$$

Caffeine is very imperfectly precipitated by the usual alkaloidal reagents. No reactions result with iodised potassium iodide and Mayer's solution, which behaviour distinguishes caffeine from nearly all other alkaloids except theobromine and colchicine. Potassio-bismuth iodide precipitates caffeine after a time from moderately dilute solutions (1 : 3000). Phosphomolybdic acid produces a yellowish precipitate, soluble in warm sodium acetate solution, the liquid depositing free caffeine on cooling. $(C_8H_{10}N_4O_2.HCl)_2PtCl_4$ is obtained on adding hydrochloric acid and platinic chloride to a highly concentrated solution of caffeine, as an orange precipitate soluble in 20 parts of cold and an even smaller quantity of warm water, crystallising again on cooling.

A solution of caffeine in 200 parts of water gives an immediate and abundant precipitate on adding a saturated solution of mercuric chloride. With a more dilute solution (1 : 1000) crystals appear in a few minutes, and in an hour or two an abundant crop of large acicular crystals is obtained. With a solution of caffeine in 4000 of water crystals appear after a few days. The precipitate contains $C_8H_{10}N_4O_2,HgCl_2$, and is much less soluble in excess of the reagent than in pure water. Hence the best results are obtained by adding an equal measure of a concentrated solution of mercuric chloride to the liquid to be tested. The compound is soluble in about 260 parts of cold water, and more readily in hot, crystallising out again on cooling. It also crystallises from hot alcohol. The

[1] The name cholestrophane is due to Stenhouse, and has reference to the resemblance the crystals have to cholesterin (Vol. II. page 312).

compound is not sufficiently insoluble to be applicable to the quantitative precipitation of caffeine (R. H. Davies, *Pharm. Jour.*, [3], xxi. 253).

Gallotannic acid precipitates moderately dilute solutions of caffeine, the precipitate being somewhat soluble in excess of the reagent. A difference of a few degrees in temperature greatly alters the solubility, and hence a solution of properly adjusted strength may be perfectly limpid at one temperature, and become completely opaque from separation of amorphous caffeine gallotannate on cooling a few degrees. A similar separation of caffeine tannate is the cause of an infusion of tea becoming turbid on cooling.

SALTS OF CAFFEINE.

Caffeine is a very feeble base. Its aqueous and alcoholic solutions have no action on litmus, and it is extracted from aqueous liquids by benzene and chloroform, even in presence of a free mineral acid. This behaviour is doubtless due to the facility with which the majority of caffeine salts are decomposed on dilution. They are decomposed by alcohol and ether as by water, and the salts with volatile acids (*e.g.*, acetic) are decomposed on exposure to air. The hydrochloride leaves merely free caffeine on exposure to 100° C. The author found that on adding free caffeine to hot water containing a trace of sulphuric acid and coloured with methyl orange, the red colour of the liquid was immediately destroyed, proving neutralisation of the acid; but an acid reaction was re-established when standard acid had been added equivalent to only about $\frac{1}{20}$ of the caffeine present. Owing to these facts, certain devises have to be employed for the preparation of the majority of the salts of caffeine. The *oxalate*[1] and *salicylate* are sparingly soluble, and can be readily prepared by mixing equivalent quantities of the acid and alkaloid in aqueous solution. The *citrate* is best obtained by mixing a chloroformic solution of caffeine with an alcoholic solution of citric acid, and evaporating the mixture to a syrup. When molecular proportions of caffeine and a mineral acid are mixed together in presence of excess of water, no combination ensues. If the quantity of water is insufficient to dissolve the alkaloid, the latter remains suspended in the liquid in an unchanged condition. If the liquid is allowed to evaporate spontaneously, the acid ultimately becomes sufficiently concentrated to act on a portion of the caffeine, and a true salt crystallises out, intermingled

[1] Caffeine oxalate is said by Leipen to be an exceptionally stable salt. It can be recrystallised from water; but the author found that the whole of the caffeine could be removed by chloroform from an aqueous solution containing a considerable excess of oxalic acid.

with crystals of the unaltered alkaloid. But as the acid is weakened by its combination, the formation of the salt is retarded till further concentration has taken place. Hence the change is progressive and continuous, the caffeine gradually dissolving and again crystallises out as a salt, though at the very last crystals of the uncombined base can be observed in admixture with the increasing crop of the true salt. By employing a considerable excess of acid the process is greatly hastened, and a product free from uncombined alkaloid is obtainable. With an excess of acid, and at a sufficient degree of concentration, the alkaloid will momentarily dissolve to a clear solution, and then almost immediately crystallise out as salt.

The foregoing observations are due to H. W. Snow (*Pharm. Jour.*, [3], xxi. 1185), who gives the following as the composition of the principal salts of caffeine:—

Caffeine hydrochloride, . .	$B,HCl+2H_2O$
Caffeine hydrobromide, . .	$B,HBr+2H_2O$
Caffeine nitrate, ...	$5(B,HNO_3)+H_2O$
Caffeine sulphate (normal), . .	B,H_2SO_4
Caffeine oxalate, . . .	$B_2,H_2C_2O_4$
Caffeine salicylate, . . .	$B,HC_7H_5O_3$

Caffeine hydrochloride crystallises in colourless prismatic needles. It loses the whole of its acid at 75° C. The *sulphate* is deposited from a hot alcoholic solution in shining needles unchanged at 100°. Caffeine *nitrate* forms fine transparent crystals, which when dropped into water become opaque, and are converted into pseudomorphs consisting of microscopic needles of free caffeine.

Caffeine citrate is official in the *British Pharmacopœia* of 1885, where the formula $C_8H_{10}N_4O_2,H_3C_6H_5O_7$ is ascribed to it. The B.P. article is generally regarded as an indefinite, unstable, inaccurately described, and superfluous preparation (*Pharm. Jour.*, [3], xix. 252). Free caffeine has not unfrequently been sold as the citrate. The proportion of acid can be directly ascertained in the citrate and other caffeine salts by titrating the solution with a standard caustic alkali (or preferably baryta) and phenolphthaleïn, and the total caffeine can be isolated by agitating the neutralised or original aqueous solution with chloroform. On treating the dry substance with cold chloroform, only the uncombined caffeine, if any, will be dissolved out (J. U. Lloyd).

A strong and stable solution of caffeine can be readily prepared by dissolving it in benzoate, cinnamate, or salicylate of sodium or ammonium. Such solutions are employed for hypodermic injections, and caffeine phenate and phthalate have been applied to the same purpose.

ISOLATION AND DETERMINATION OF CAFFEINE.

None of the compounds of caffeine are sufficiently stable or insoluble to be of service for the separation or precipitation of the alkaloid, which is always determined by weighing it in the free state. The *isolation* of caffeine presents no difficulty, and may be effected by a variety of methods. The majority of these depend on the treatment of the substance or its aqueous infusion with lime, magnesia, litharge, or basic lead acetate, to render the tannin &c., insoluble; and crystallisation of the caffeine from the concentrated filtrate, or extraction of it by benzene, ether, or chloroform. To ensure the absence of inorganic salts, the alkaloid should be sublimed or shaken out from its aqueous solution by chloroform. Provided that the caffeine isolated be well crystallised, colourless, free from acid or alkaline reaction to litmus, completely soluble in chloroform, exerts no reducing action on Fehling's solution, and leaves no ash on ignition, it may be regarded as pure.

Although the isolation of caffeine in a state of absolute purity may be easily effected, the accurate *determination* of the proportion of alkaloid present, especially in tea, is attended with great difficulty, and hence most of the published results represent the proportion of caffeine *isolated*, rather than the amount existing in the substance examined. When once in solution, several methods may be used, though even in this case some of the published processes give results which are very gravely wide of the truth. As a consequence, the great majority of the published determinations of caffeine are completely worthless, and even where a number of figures have been obtained by the same process they do not necessarily bear any definite relation to each other.

The determination of the alkaloid in tea has recently been the subject of a very large number of experiments in the author's laboratory by C. M. Caines, G. S. A. Caines, and G. E. Scott Smith (*Pharm. Jour.*, [3], xxiii. 215). The following facts have been fully established:—

1. Aqueous solutions of caffeine, even when very dilute, may be concentrated by boiling, and subsequently evaporated to dryness at 100° without the least loss of alkaloid (see page 477).

2. Caffeine may be completely dehydrated at 100° in the water-oven. It undergoes no appreciable loss by volatilisation when exposed to 100° for many hours; but sublimation to a minute extent can be proved by the aid of the microscope (see page 476).

3. Caffeine cannot be estimated, even approximately, by crystallisation from water, the amount which remains obstinately in solution, in the presence of saline matters, often exceeding that which can be separated as crystals.

4. Caffeine can be completely extracted from its acidulated or slightly ammoniacal aqueous solutions by repeated agitation with chloroform. In the author's experiments, from a solution slightly acidulated with sulphuric acid, the first treatment with chloroform extracts from 70 to 85 per cent. of the total alkaloid. Four *treatments with chloroform usually effect the complete extraction* of the alkaloid; but it is desirable to agitate a fifth time and evaporate the separated solvent apart, to prove that no more caffeine is being dissolved. In this last case, the solution may be advantageously rendered ammoniacal, or a loss of 0·001 to 0·002 gramme of caffeine may occur, probably owing to the existence of traces of caffeine sulphate, especially where the solution is strongly acidulated with sulphuric acid. On distilling the chloroformic solution of caffeine, and drying the residue at 100° C., the alkaloid is obtained in a perfectly anhydrous condition.

5. Charcoal cannot be employed for decolorising caffeine solutions, without a considerable absorption of alkaloid, which is retained with extreme persistency. If the caffeine isolated be coloured, it may be dissolved in a little hot water, and the filtered solution evaporated to dryness; but there is little difficulty in isolating the alkaloid in a snow-white condition.

6. Caffeine is completely unchanged by heating to 100° with strong hydrochloric acid, or with sulphuric acid diluted with one-third of its measure of water. On treating the mixture with water, the whole of the alkaloid may be recovered by agitation with chloroform, as in 4.

7. Caffeine is readily decomposed by alkalies. By warming with dilute caustic soda, it easily undergoes change, and by boiling with lime it is partly decomposed, with formation of ammonia and methylamine (see page 479).

8. When commercial caffeine is treated with ignited magnesia and water, and the mixture distilled, a slight but distinct formation of ammonia is observed, apparently accompanied with traces of volatile amines. But the volatile bases are found chiefly in the first fractions of the distillate, the latter portions being quite free from alkaline reaction; and when carefully purified caffeine is employed, the formation of ammonia and other volatile bases is reduced to a minute trace. Hence their formation is more probably due to the decomposition of some impurity present in small quantity than of the caffeine itself, as in the latter case the production would continue throughout the distillation. On filtering from the magnesia and extracting the filtrate with chloroform, the original weight of caffeine can be recovered, if the pure alkaloid was originally employed.

9. If a mixture of caffeine with magnesia be made into a paste with water and dried, the alkaloid can be wholly extracted from the mixture by prolonged treatment with chloroform.

10. When one part of caffeine is dissolved in hot water, and a solution of two parts of gallotannic acid added, the caffeine can be accurately determined by precipitating the solution with lead acetate and extracting the concentrated filtrate with chloroform. If the liquid be concentrated to a syrup, mixed with ignited magnesia, and dried at 100°, the whole of the alkaloid cannot be extracted by boiling the powdered mass with dry chloroform, however long the treatment be continued. If tannin prepared from tea be substituted for gallotannic acid in the foregoing experiment, a similar result is obtained.

11. When a decoction of tea is substituted for the foregoing artificial mixture of caffeine with excess of tannin a precisely similar result is obtained. Whether sand or magnesia be used, the alkaloid is only partially extracted, even after prolonged boiling with chloroform or ether.[1] Thus, decoctions prepared by

[1] The following experiments were made by G. E. Scott Smith in the author's laboratory. Fifty grammes weight of commercial black tea of medium quality was powdered and boiled with water for thirty minutes. The solution was filtered and made up to 1 litre after cooling. Aliquot parts of the solution were then treated in the following manner.

A. 100 c.c. (=5 grammes of tea) was evaporated to a syrup and mixed with 5 grammes of ignited magnesia. The mixture was dried thoroughly at 100°, powdered, and boiled with ether free from alcohol and water.

Caffeine extracted by	6	hours' treatment, . . .	0·059 gramme.
,, ,,	4	hours' further treatment, . .	0·009 ,,
,, ,,	3	hours' ,, ,, . .	0·001 ,,
Total, .	13		0·069 = 1·38 per cent.

On subsequently boiling the residue with alcohol an additional 0·0605 gramme of caffeine was extracted, making 2·59 per cent. in all.

B. Was conducted like A, but dry chloroform was substituted for ether. The total caffeine extractable by chloroform was 1·54 per cent.

C. Conducted like A, but rectified spirit was employed at once. It extracted 2·81 per cent. of brownish caffeine, which was reduced to 2·78 per cent. by re-solution in water and extraction with chloroform.

D. Conducted like B, but sand was substituted for magnesia. Treatment with dry chloroform extracted successively 0·0365, 0·0175, 0·0135, and 0·0010 gramme of caffeine during nine hours' treatment. On subsequent treatment with alcohol much tannin and colouring matter was extracted. This was precipitated by lead acetate, and the concentrated filtrate shaken with chloroform. Additional yield, 0·070 gramme, making a total yield of 2·77 per cent. Why a portion of the caffeine but not the whole should be extracted by chloroform in the absence of magnesia is not evident.

E. 100 c.c. (=5 grammes tea) was heated to boiling, treated with solid

boiling two separate samples of black tea with water were each divided into two equal parts. One of these was precipitated by lead acetate, and the caffeine recovered from the filtered and concentrated liquid by repeated agitation with chloroform. The other halves were evaporated to dryness with magnesia and the powdered residue thoroughly exhausted by boiling with chloroform, and subsequently boiled with alcohol for a long time.

	Sample A. 30 Minutes' Boiling.	*Sample B.* 20 Minutes' Boiling.
Lead process, ...	3·31 per cent.	2·07 per cent.
Magnesia process: by chloroform, . .	1·18 ,,	0·90 } 2·06 per cent.
,, ,, by alcohol, . . .	......	1·16 }

In other experiments with mixtures of caffeine, tea-tannin, and excess of magnesia, from 8 to 10 per cent. of the alkaloid was not extractable either by chloroform or alcohol, but could be recovered by treatment with water.

12. When finely-powdered tea is mixed with slaked lime, ignited magnesia, or sand, made into a paste with hot water, and the mixture thoroughly dried at 100°, only a fraction of the total alkaloid can be extracted with chloroform,[1] however carefully the process be conducted. On subsequently treating the mixture with alcohol, the greater part of the remaining caffeine is ultimately dissolved, but prolonged treatment by boiling alcohol is necessary to extract the caffeine from a mixture of tea-extract or powdered tea with magnesia, and complete extraction is always doubtful.

13. When a decoction of tea is treated with basic or neutral acetate of lead a voluminous precipitate is formed. If an aliquot part of the liquid be filtered, concentrated, and treated with sulphuretted hydrogen, sulphurous acid, sulphuric acid, or sodium phosphate, to remove the excess of lead, and again filtered, the caffeine may be extracted in a condition of perfect whiteness and purity by agitation with chloroform.

lead acetate, filtered, and an aliquot part of the filtrate concentrated, freed from lead, and shaken repeatedly with chloroform. Caffeine was recovered equivalent to 2·63 per cent. of the tea.

[1] The remarkable fact of the retention of the caffeine of tea by lime or magnesia in a form incompletely dissolved by chloroform was first observed by B. H. Paul and G. E. Scott Smith (*Pharm. Jour.*, [3], xxi. 882). Little more than one-third of the total caffeine was extractable by chloroform from the lime mixture, and little more than one-half from the magnesia mixture. By subsequent treatment with alcohol the remaining caffeine was dissolved.

14. By prolonged boiling with litharge a decoction of tea becomes completely decolorised, but the process is tedious. If after a time a small addition of lead acetate be made, clarification occurs in a few minutes, and an aliquot part of the liquid may be filtered and treated as in 13.

From the foregoing statements (10, 11, 12, 13) it is evident that the determination of caffeine when in a state of solution presents no great difficulty, though the widely-used plan of evaporating the liquid with sand and lime or magnesia, and extracting the dried mixture with chloroform or ether, gives gravely inaccurate results. The great difficulty in determining the total caffeine present in tea is the obstinacy with which a portion of the alkaloid is retained by the vegetable tissue, a fact which suggests that it exists partly in some insoluble combination only gradually decomposed by boiling water or alcohol.[1]

This form cannot be mere tannate of caffeine, as that compound is moderately soluble in boiling water. It is more probable that the caffeine itself is a product of the hydrolysis of a more complex body, possibly a glucoside.[2] This conjecture receives considerable support from the recent experiments of E. Knebel (*Apoth. Zeit.*, 1892, vii. 112), who states that the caffeine in the kola-nut exists as a glucoside, kolanin, which, on boiling with water, or treatment with dilute acids, splits up into caffeine, glucose, and kola-red, $C_{14}H_{13}(OH)_5$.

On the supposition that the cellular structure of the tea is the cause of the obstinate retention of the caffeine, Zöller (*Zeitsch. Anal. Chem.*, xii. 106) has proposed to treat the finely-powdered tea with strong sulphuric acid diluted with one-third of its

[1] The following figures, obtained in the author's laboratory, show the rate of exhaustion on treating powdered black tea with hot and cold water:—

Caffeine extracted by Cold Water.		*Caffeine extracted by Boiling Water.*	
In 3 days,	1·81 per cent.	In ½ hour,	2·46 per cent.
Additional 2 days,	0·29* ,,	In additional 2 hours,	0·72 ,,
,, 2 days,	0·70* ,,	,, 4 hours,	0·16 ,,
,, 6 days,	0·22 ,,	,, 6 hours,	0·01 ,,
,, 6 days,	0·13 ,,		
Total in 19 days,	3·15 ,,	Total in 12½ hours,	3·35

* These two figures have not been transposed.

Thus the extraction of the caffeine by boiling water was practically complete after 6 hours' treatment, while with cold water the total amount was not dissolved after 19 days' treatment.

In both the hot and cold water experiments, the infusion reduced Fehling's solution after removal of the tannin by lead acetate. The caffeine did not reduce the copper solution either before or after boiling with dilute acid.

[2] The author has proved the presence of a glucoside in some teas.

measure of water, and heat the mixture at 100°, till the cells are thoroughly broken up. Some water is then added, an excess of hydrated oxide of lead stirred in, and the mixture dried and exhausted with alcohol of 86 per cent. The alcoholic solution is decolorised with animal charcoal, and evaporated till caffeine crystallises on cooling. From the mother-liquor, the residual caffeine is extracted by ether. Zöller obtained the high proportion of 4·92 per cent. of caffeine from a high quality of Himalayan tea, in addition to an appreciable quantity of theobromine.

The author has made a number of experiments on the lines of Zöller's process, modified in various manners, but, chiefly through the remarkable persistency with which caffeine is absorbed and retained by the carbon formed by the acid treatment, they have not hitherto resulted in the evolution of a practical analytical method.[1]

[1] On treating powdered tea with slightly diluted sulphuric acid, and heating the mixture in the water-oven for an hour or two, a black product is obtained which powders readily. On boiling this product with water, a perfectly colourless solution is obtained, from which, after concentration, perfectly colourless caffeine is extracted by agitation with chloroform, either with or without previous removal of the sulphuric acid by boiling with litharge or white lead, or neutralisation with ammonia. The fact that a colourless liquid is obtained on treating the charred tea with water is due to the absorption of the colouring matters by the finely-divided carbon formed. Unfortunately, this product also takes up a considerable proportion of the caffeine, and retains it with such obstinacy that it is only extracted by prolonged and repeated treatments with alcohol. Although the entire amount present is ultimately obtainable in solution, the extraction is too uncertain and tedious to render the method a desirable one in practice. Exhaustion direct with alcohol, ether, chloroform, benzene, or water, either with or without previous neutralisation of the acid with litharge or magnesia, equally failed to ensure ready extraction. Of the numerous experiments made in this direction the following may be mentioned. Twenty-five grammes of ordinary black tea of medium quality was finely powdered, and treated with 10 c.c. of sulphuric acid diluted with one-fifth of water. The mixture was heated at 100°, treated with a little water, and ground with excess of litharge till neutral. The mixture was redried, and thoroughly exhausted successively in a Soxhlet-tube with boiling rectified spirit, boiling proof-spirit, and boiling water. The solutions were evaporated, and the caffeine extracted by repeated agitation with chloroform. The following were the results obtained:—

	Yield of Caffeine.
By strong alcohol (sp. gr. ·838), ...	3·03 per cent.
By subsequent treatment with proof-spirit, ...	0·50 „
By subsequent treatment with water, ...	0·21 „
Total, ...	3·74 „

The caffeine isolated was snow-white. These results show that the alkaloid is unaltered by the treatment, and if extraction could be effected with certainty

As the result of very numerous experiments, the author gives the preference to the following method of extracting and determining the caffeine in *tea*. It closely resembles a process employed by S t a h l s c h m i d t (*Chem. Centralblat*, 1861, 396):—Six grammes of finely-powdered tea is treated in a flask with 500 c.c. of water, which is then kept boiling under a reflux condenser. No Soxhlet extractor or similar arrangement is so effective or rapid as actual boiling with the water. Alcohol effects no quicker or better extraction than water, and has the disadvantage of dissolving chlorophyll. After six or eight hours' boiling, the decoction may be filtered, the residue washed on the filter, and the filtrate made up with water to 600 c.c. It is then heated nearly to boiling, and about 4 grammes of acetate of lead in powder added, a reflux condenser attached, and the liquid boiled for ten minutes. If on removing the source of heat the precipitate does not curdle and settle readily, leaving the liquid colourless, or nearly so, a further addition of lead acetate must be made and the boiling repeated. When clarification is effected, the liquid is passed through a dry filter. Five hundred c.c. of the filtrate (=5 grammes of tea) is then evaporated to about 50 c.c., when a little sodium phosphate is added to precipitate the remaining lead. *The liquid is filtered, the precipitate washed, and the* filtrate further concentrated to about 40 c.c., when the caffeine is extracted by repeated agitations with chloroform, at least four treatments with which are necessary to ensure the complete extraction of the alkaloid.[1] The separated chloroform solutions are mixed, and distilled in a tared flask immersed in boiling water. The last traces of chloroform are removed while the flask is still hot by a current of air, and the residual alkaloid is weighed. The caffeine thus isolated is snow-white in colour, neutral in reaction to litmus, and completely volatile and soluble in water. It does not reduce Fehling's solution either before or after boiling with dilute acid.

As a precaution, the exhausted tea-powder should be again boiled with water, and the decoction treated as before. When experience has proved this to be unnecessary, the process can be shortened by boiling the tea with 600 c.c. of water in the first place, and adding lead acetate without previously filtering from the exhausted tea. This modification becomes necessary in the case of

by a single solvent, the process would possess marked advantages. Substitution of magnesia for the oxide of lead, and various other modifications of the details equally failed to give a satisfactory result.

[1] In the great majority of cases the chloroform separates readily. Should an obstinate emulsion be formed, the best plan is to place the mixture in a flask, distil off the chloroform, treat the residual liquid with a few drops of basic acetate of lead, filter, and agitate the filtrate again with chloroform.

certain teas (*e.g.*, gunpowder), the aqueous decoctions of which filter very slowly.

The following results by the above process were obtained by C. M. Caines in the author's laboratory (*Pharm. Jour.*, [3], xxiii. 218). In some instances the caffeine extracted by half an hour's boiling was determined, in addition to the total amount obtained by six hours' boiling with water. The results refer to the moisture-free teas, which were representative commercial samples:—

Description of Tea.	Tannin; by Lead Acetate.	Caffeine.	
		Extracted in 30 minutes.	Total; extracted in 6 hours.
Ceylon, whole leaf (Pekoe),	13·01 per cent.	3·40 per cent.	3·85 per cent.
Ceylon, broken leaf, . .	12·31 ,,	...	4·03 ,,
Assam, whole leaf (Pekoe),	10·08 ,,	...	4·02 ,,
Assam, broken leaf, . .	11·33 ,,	...	4·02 ,,
Java Pekoe, . . .	12·93 ,,	...	3·75 ,,
Kaisow, red leaf, . .	11·35 ,,	...	3·41 ,,
Moning, black leaf, . .	11·76 ,,	3·44 ,,	3·74 ,,
Moyune Gunpowder, . .	12·95 ,,	2·76 ,,	2·89 ,,
Natal Pekoe-Souchong, .	9·90 ,,	2·71 ,,	3·08 ,,

The foregoing process is applicable to the determination of the caffeine in *coffee*, of which 12 grammes may be conveniently employed. In the presence of chicory the extracted alkaloid is liable to be strongly coloured, in which case it should be redissolved in water, a few drops of caustic soda added, and the liquid again exhausted with chloroform.

An alternative process for the determination of caffeine in *tea* is that of Paul and Cownley (*Pharm. Jour.*, [3], xviii. 417), which in some respects resembles a method described by Versmann (*Arch. Pharm.*, [2], lxviii. 148), and with certain modifications communicated to the author by A. J. Cownley is as follows:—Five grammes weight of finely-powdered tea is well mixed in a mortar with 2 grammes of ignited magnesia, the mixture thoroughly moistened with hot water, again triturated, and then dried at 100°. It is next extracted with boiling alcohol,[1] and the resultant liquid evaporated nearly to dryness. The residue is boiled with 50 c.c. of water, and treated with a few drops of dilute sulphuric acid. When cold, the liquid is filtered and repeatedly shaken with chloroform

[1] Experiments made in the author's laboratory showed that even with the most careful treatment it is difficult to ensure complete extraction of the caffeine, a small additional quantity being subsequently obtained by treatment with water.

until exhausted.[1] The united chloroform solution is then agitated with a very dilute solution of caustic soda, which removes a little colouring matter, so that on subsequently distilling off the chloroform in a weighed flask, the caffeine is obtained perfectly pure and colourless, or at most with a faint green tinge.

By the foregoing process, Paul and Cownley (*Pharm. Jour.*, [3], xviii. 417) found Indian and Cingalese teas to contain a much larger percentage of caffeine than, owing to the faulty methods of analysis employed, is commonly supposed. The proportion of alkaloid isolated from commercial samples of all qualities, and containing from 3·6 to 6·8 per cent. of moisture, ranged from 3·22 to 4·66 per cent. on the tea in its commercial condition (equal to 3·57 to 4·99 per cent. in the moisture-free tea), and bore no relation to the so-called "strength" of the tea. Java tea approached Ceylon tea in the proportion of caffeine present (2·94 to 3·78 per cent.), but China and Japan teas were generally poorer in alkaloid, the proportion in these products ranging (for a limited number of samples) from 2·20 to 3·46 per cent. J. H. Small obtained, by Paul and Cownley's method of assay, from 1·79 to 2·30 per cent. of caffeine from Japanese teas, and from 2·38 to 3·54 per cent. from Chinese and Indian teas.

Paul and Cownley have also employed the foregoing method of determining caffeine for the assay of *coffee* (*Pharm. Jour.*, [3], xvii. 565, 648). The caffeine obtained by evaporation of the chloroform is liable to contain a small quantity of a brownish waxy or resinous impurity, and hence should be purified by re-solution in boiling water, and recovered by evaporating the filtered solution and drying the residual alkaloid at 100°. By this process they found the proportion of caffeine in coffee-berries to vary within comparatively narrow limits, and not to be materially affected by roasting. Hence they recommend the determination of the alkaloid in commercial coffee as a means of estimating the proportion of chicory or other admixture present.

Theobromine. Dimethyl-xanthine.

$$C_7H_8N_4O_2; \text{ or, } C_5H_2(CH_3)_2N_4O_2.$$

The constitution and synthesis of theobromine have already been described (page 473). It is the lower homologue of caffeine, to which alkaloid it presents a close general resemblance, but differs considerably from it in its solubilities.

[1] In Paul and Cownley's experience, six or seven successive treatments with chloroform (using from 30 to 40 c.c. each time) are necessary to effect the complete extraction of the caffeine from the solution yielded by 5 grammes of tea.

Theobromine is isomeric with theophylline and paraxanthine.

Theobromine exists naturally in cocoa, the seed or bean of *Theobroma cacao*; and together with caffeine in the kola nut (*Sterculia acuminata*). An alkaloid apparently identical with theobromine was found by Zöller in a specimen of Himalayan tea.

Theobromine forms a white, crystalline powder, which under the microscope appears as trimetric needles and club-shaped groups. When heated to about 290° it sublimes without decomposition or previous fusion.

Theobromine has a very bitter taste, which is only slowly developed. Its physiological action is similar to that of caffeine, but more powerful. In large doses it produces well-defined poisonous effects. It is eliminated by the kidneys, and can be detected in the urine.

Theobromine dissolves in 1600 parts of ice-cold or 148 of boiling water. In cold alcohol also it is only very slightly soluble (1 in 4280), and requires fully 400 parts at the boiling-point, but dissolves far more easily in 80 per cent. spirit. It requires 1700 parts of cold or 600 of boiling ether for solution, dissolves in 105 parts of boiling chloroform, is soluble in amylic alcohol, dissolves slightly in benzene, and is insoluble in petroleum spirit.

Theobromine dissolves in acids, and is precipitated from the solution by alkalies, but is soluble in excess of ammonia or fixed alkalies. It is wholly extracted from its solution in caustic soda by agitation with chloroform.

Theobromine is a weak base, its salts being readily decomposed by water with separation of the alkaloid (compare Caffeine, page 482). The *hydrochloride*, $BHCl + H_2O$, and *nitrate*, $BHNO_3$, lose all their acid at 100°. $B_2H_2PtCl_6 + 2H_2O$ crystallises in oblique prisms, which effloresce in the air and become anhydrous at 100°. $BHAuCl_4$ forms tufts of yellow needles.

An aqueous solution of theobromine forms with mercuric chloride a white crystalline precipitate, sparingly soluble in water and alcohol.

One of the most definite and insoluble compounds of theobromine is that with nitrate of silver. When a very dilute aqueous solution of theobromine nitrate is treated with silver nitrate, silver-white needles containing $C_7H_8N_4O_2,AgNO_3$ form after a short time. The compound is only sparingly soluble in water, and may be dried without change at 100°. If a solution of theobromine in ammonia be treated with nitrate of silver, a gelatinous precipitate is obtained which dissolves easily in warm ammonia, and on boiling the solution for some time hydrated silver theobromine, $C_7H_7AgN_4O_2$, separates as a granular nearly insoluble precipitate.

Theobromine reacts with alkalies like a weak acid and forms definite salts. Thus the *sodium salt* is obtained by adding theobromine to soda-lye until a portion remains undissolved after long standing, and evaporating the filtrate under the air-pump. The product is destitute of crystalline structure, is extremely soluble in water, has a strong alkaline reaction, and absorbs carbon dioxide from the air. The *barium salt*, $(C_7H_7N_4O_2)_2Ba$, separates on adding theobromine to baryta-water as a mass of microscopic needles, and is obtainable as a snow-white felt of silky needles by slowly cooling its solution in hot water. If the solution be rapidly cooled, it solidifies to a stiff jelly.

Theobromine yields no product similar to caffeidine when boiled with concentrated baryta-water or caustic alkalies. By such treatment, as also when heated with hydrochloric acid under pressure to 240°, theobromine gives the same products as caffeine (page 478).

The best precipitant of theobromine is a solution of sodium phosphotungstate (page 136), which should be added to a solution strongly acidulated with sulphuric or nitric acid. The yellow precipitate should be mixed with sodium carbonate or magnesia, dried, and the mixture exhausted with chloroform, which dissolves the theobromine.

When theobromine is heated with dilute sulphuric acid and lead dioxide, carbon dioxide is evolved. When once started, the reaction continues without further application of heat, and if excess of the oxidising agent and too long heating be avoided the filtered liquid is colourless, but evolves ammonia on treatment with a caustic alkali, separates sulphur from sulphuretted hydrogen, colours the skin purple-red, and immediately turns blue when treated with a moderate quantity of magnesia. Excess of magnesia destroys the colour, which may be restored by cautious addition of sulphuric acid.

By oxidation with chromic acid mixture, theobromine yields carbon dioxide, methylamine, and methyl-parabanic acid, $C_3H(CH_3)N_2O_3$.[1] Aqueous chlorine converts it into methyl-urea, $CH_3(CH_3)N_2O$, and methyl-alloxan, $C_4H(CH_3)N_2O_4$; while treatment with hydrochloric acid and potassium chlorate oxidises it to dimethyl-alloxantin, $C_8H_4(CH_3)_2N_4O_8$. Theobromine gives with oxidising agents and ammonia the same colour-reactions which characterise caffeine (page 480).

Isolation and Determination of Theobromine.

Theobromine may be isolated by much the same methods as those

[1] Methyl-parabanic acid is easily soluble in hot water, from which it crystallises in transparent prisms, melting at 148°. Warmed with ammonia and calcium chloride, it gives a precipitate of calcium oxalate (compare Cholestrophane, page 481).

used for the determination of caffeine, having regard to the far less ready solubility of the former alkaloid in water, alcohol, and other solvents. As in the case of caffeine, the methods used by observers who have recorded high yields of theobromine are more trustworthy than those of chemists who have succeeded in isolating comparatively small proportions.

For the preparation of theobromine, E. Schmidt (*Archiv der Pharmacie*, ccxxi. 656) mixes commercial cocoa (freed as far as possible from fat by pressure) with half its weight of freshly-slaked lime, and extracts the mixture with boiling alcohol of 80 per cent. (by volume). On cooling the alcoholic extract, theobromine separates out, and on recrystallisation from hot alcohol is obtained as a white, crystalline anhydrous product.

Before extracting theobromine it is preferable to get rid of the fat by exhausting the finely-divided cocoa with petroleum spirit. The residue is made into a paste with water and ignited magnesia, dried at 100°, and exhausted with spirit of 80 per cent.

Another method of extracting the theobromine from cocoa is to exhaust the substance with water or dilute alcohol, precipitate the solution with acetate of lead,[1] separate the lead from the filtered solution by sulphuretted hydrogen, evaporate the filtrate to dryness, and extract the theobromine from the residue by boiling chloroform.

Caffeine may be separated from theobromine by treating the mixed alkaloids with cold benzene, in which theobromine is practically insoluble.

James Bell (*Foods*, i. 85) boils 100 grains of the cocoa repeatedly with benzol, which dissolves fatty matters and caffeine.[2] The residue is mixed in a mortar with 100 grains each of sand and calcined magnesia and sufficient water to form a paste, the product dried at 100°, and repeatedly boiled with strong alcohol. The solution is filtered, distilled, and the residual theobromine dried at 100° and weighed. It is freed from traces of fat and caffeine by treatment with hot benzene, and then treated twice with

[1] By using a known volume of liquid and filtering off four-fifths or other known proportion, the tedious washing of the bulky lead precipitate may be avoided. When once the alkaloid is in solution, the method recommended by the author for the determination of caffeine (page 490) is also applicable to theobromine. The chloroform should be used warm.

[2] Bell refers to this product, which was especially yielded by Trinidad cocoa, as a "theine-like alkaloid;" but as Weigmann and E. Schmidt have both proved the occurrence of caffeine in cocoa (*Annalen*, ccxvii. 306) there seems no doubt as to the nature of the substance observed by Bell. He separated it from the fatty matter by boiling with water. The aqueous liquid was evaporated, and the alkaloid purified by successive solution in water and benzene.

recovered from 41 to 41½ per cent. of theobromine from pure diuretin, 6½ per cent. remaining in the filtrate and washings. Making this allowance, the theobromine should not be less than 46½ per cent., and that isolated should melt when carefully heated, be completely volatile, and dissolve readily in caustic soda solution. From the filtrate from the theobromine, the salicylic acid can be isolated by acidulating with hydrochloric acid and agitating with chloroform. The separated chloroform is washed with water to remove mineral acid, a little water and a drop of phenolphthaleïn solution added, and the liquid then titrated with decinormal caustic alkali. Each c.c. of $\frac{N}{10}$ alkali required for neutralisation represents 0·0138 gramme of salicylic acid. Diuretin should contain 38½ per cent. of salicylic acid. The titration completed, the chloroform may be separated and evaporated, when the residue will represent the 6·5 per cent. of theobromine not previously separated, together with any caffeine the preparation may have contained. To prove the absence of caffeine in diuretin, Vulpius recommends that 1 gramme of the sample should be dissolved in 5 c.c. of water, and the solution neutralised with hydrochloric acid, when the theobromine will form a milky precipitate readily soluble in soda solution. If the mixture be shaken with its own measure of chloroform, not more than 0·005 gramme of residue should remain on evaporating the separated chloroform.

THEOPHYLLINE, $C_7H_8N_4O_2$, a base existing in minute quantity in tea, is isomeric with theobromine and paraxanthine (occurring in human urine). According to A. Kossel[1] (*Berichte*, xxi. 2164; *Pharm. Jour.*, [3], xix. 41; *Jour. Chem. Soc.*, liv. 1115), theophylline crystallises with 1 aqua, which it loses at 110°. It melts at 264°. It is easily soluble in warm water, but sparingly in cold alcohol, and is extremely soluble in very dilute ammonia. It forms a crystalline hydrochloride, nitrate, chloro-

[1] For its isolation, Kossel extracts tea-leaves with alcohol and evaporates the tincture to a syrup, when most of the caffeine crystallises out on cooling. The filtrate is diluted with water, acidulated with sulphuric acid, filtered after a considerable time, made alkaline with ammonia, and precipitated with nitrate of silver. After standing twenty-four hours the precipitate is filtered off and warmed with nitric acid; on cooling the liquid, the silver nitrate compounds of *adenine* and *hypoxanthine* (sarcine) crystallise out. The acid filtrate is treated with ammonia, and the precipitate suspended in water acidulated with nitric acid and decomposed by sulphuretted hydrogen. On concentrating the filtrate, *xanthine* first crystallises, and subsequently theophylline. The mother-liquor is precipitated with mercuric nitrate, the free acid being nearly neutralised with soda. The precipitate is then separated, suspended in water, and decomposed by sulphuretted hydrogen, and the theophylline recovered from the filtrate.

platinate, auro-chloride, and mercuro-chloride, and combines with soda to form a readily soluble compound. When evaporated with chlorine-water, theophylline yields a scarlet residue, changed to violet on addition of ammonia. The *silver-derivative*, $C_7H_7A_gN_4O_2$, is obtained as an amorphous precipitate on adding silver nitrate to an aqueous solution of theophylline. It crystallises from hot ammonia, and dissolves readily in nitric acid. The methyl-derivative, $C_7H_7MeN_4O_2$, prepared by heating the last substance with methyl iodide and methyl alcohol, melts at 229°, and is identical with caffeine.

Tea.[1]

The tea of commerce is the prepared leaf of *Thea sinensis* (and perhaps allied species), a shrub-like plant belonging to the genus *Camellia.* It occurs native in the Himalayas and Assam, has long been cultivated in China and Japan, and is now raised largely in British India, Ceylon, Brazil, &c.[2]

It was formerly believed that green and black teas were the product of distinct plants, but it is now known that the difference is due to the method of preparation; black tea having undergone a certain amount of fermentation, whereas in green tea this change is carefully prevented.[3] The leaves are gathered from the plants four times a year, and are distinguished according to their age. Each leaf is at first a "flowery Pekoe" leaf, which is the name applied to the leaf-bud. This becomes in succession "orange

[1] French; *le Thé.* German; *der Thee.*

[2] The Report of H.M. Customs for 1891 to 1892 states that the weight of tea imported from the peninsula of Hindostan showed a decrease of three million pounds, while that from Ceylon increased by more than sixteen millions of pounds, exceeding for the first time that of China tea, which now forms only one-fourth of our entire consumption.

[3] "For *black teas*, the leaves are withered a little, rolled to liberate the juices, left in balls for the proper state of fermentation, then sun-dried and subjected to a careful firing in a furnace. For *green teas*, the fresh leaves are first withered in hot pans, then rolled to free the juices, slightly roasted in the pans, sweated in bags, and returned to the pans for a final slow roasting, with stirring, for eight or nine hours, beginning at the temperature of 160° F., and falling to 120° F. at the close" (A. B. Prescott). The methods of preparing tea vary materially in different countries. In India, the manufacturing processes are very much simplified, being reduced to five, instead of the twelve practised in China. In addition, the work is nearly all accomplished by machinery, so that the leaves are not touched by the labourers, except in picking. This is partially true also of Japanese tea, whereas Chinese tea is manipulated almost entirely by hand, except when the feet are employed. A detailed description of the method of preparing Japanese tea has been given by J. Takyama (*Chem. News*, l. 299).

Pekoe," "Pekoe," "Souchong 1st," "Souchong 2nd," "Congou," and finally "Bohea."[1] In some cases the leaves are classified simply as Pekoe, Souchong, and Bohea. The first and second pickings of the season furnish the finest teas; but the quality of the product depends on the age of the tree as well as the age of the leaf; the finest teas being produced from the young leaves of young plants, whilst old leaves, and the leaves of old wood, are deficient both in flavour and extract.[2]

Besides the foregoing distinctions, based on the age of the leaf, there are other classifications based on the district of growth and the method of preparation. Thus among the chief commercial varieties of *black* tea are Assam, Ceylon, Japan, Kaisow, Moning, and Oolong; and those of *green* tea, Gunpowder, Hyson, Young Hyson, Imperial, and Twankay. Green tea has much declined in popularity of late years. "Caper tea" is always more or less of a factitious character.

Very few trustworthy complete analyses of tea have been published; and, indeed, they have but a limited interest or practical value, since the tea is not consumed as a whole, but invariably infused, and the infusion contains the tea-constituents in very different proportions from those in which they exist in the leaf.

An average of sixteen analyses of tea made by König showed:—Moisture, 11·49 per cent.; caffeine, 1·35; albuminous

[1] *Pek-ho* signifies "white hairs;" *Sou-chong*, "little plant;" and *Con-gou*, "labour."

[2] O. Kellner (*Land. Versuchs-Stat.*, 1886, 370; *Jour. Chem. Soc.*, lii. 73) has published analyses of the leaves of the same tea-plant during six months (May to November). His figures show a decrease in the proportion of total nitrogen, and almost entire disappearance of amido-nitrogen in the older leaves. The caffeine fell from 2·85 to 1·00 (estimated by evaporating the infusion to dryness with magnesia, and extracting with ether), and the tannin rose from 8·53 to 12·16. The hot-water extract remained practically stationary, while the ether-extract rose from 6·48 to 22·19. The ash increased from 4·69 to 5·04 only, but in July fell to 4·29, and in September reached 5·11. All the ash determinations are improbably low, and suggest ignition at too high a temperature. Such an error would vitiate the potash determinations, which showed a variation from 49·06 in May to 17·31 in November. The manganese (Mn_3O_4) ranged from 1·21 to 2·48, and the chlorine from 1·04 to 1·56 per cent. of the ash.

The albuminoids were determined by a modification of Stutzer's process. The aqueous decoction of 2 grammes in 100 c.c. of water was treated with 20 c.c. of a 10 per cent. solution of cupric sulphate, and a titrated solution of caustic soda in such quantity as to leave a little copper in solution. The liquid filtered rapidly, and was free from albuminoids. The precipitate was washed first with hot water and then with strong alcohol. The contained nitrogen was determined by ignition with soda-lime.

matters, 22·22; ethereal oil,[1] 0·67; gum and dextrin, 7·13; tannin, 12·36; fat, wax, and chlorophyll, 3·62; other nitrogen-free matters, 16·75; woody fibre, 20·30; and ash, 5·11 per cent.

J. M. Eder (*Dingl. Polyt. Jour.*, ccxxxi. 445, 526) gives the following as the average composition of tea.[2]

A. Soluble in water—	Per cent.
Moisture,	10·0
Tannin,	10·0
Gallic acid, oxalic acid, and quercetin,	0·2
Boheic acid,	0·1
Caffeine or theine,	2·0
Tea oil,	0·6
Albuminous bodies (probably legumin),	12·0
Gummy substances, dextrin, and sugar,	3 to 4
Mineral matters,	1·7

B. Insoluble in water—	Per cent.
Chlorophyll,	1·8 to 2·2
Wax,	0·2
Resin,	3·0
Colouring matter,	1·8
Extractive matter, mostly soluble in nitric acid,	16·0
Cellulose,	20·0
Albuminous bodies,	12·7
Mineral matters,	4·0

[1] Essential Oil is determined by distilling a considerable quantity of tea (200 grammes) with 1500 c.c. of water, and agitating the distillate with ether. On distilling off the ether the tea oil remains. Eder found 0·52 per cent. of oil in gunpowder and 0·41 per cent. in pekoe bloom tea by this process. Battershall employs 10 grammes of tea, and saturates the distillate with calcium chloride before agitating with ether. A good sample of black tea yielded 0·87 per cent. of volatile oil when examined by this method.

Tea oil is a bright yellow liquid, which darkens and resinifies on exposure to the air for a few days, and turns reddish brown with nitric acid. Even on exposing the aqueous distillate from tea to the air for some time, it loses its aromatic odour, and little or no oil can then be separated from it by ether, and even if the distillate be kept in closed vessels the aroma is soon lost. These facts explain the fact that tea leaves lose their bouquet by age or exposure.

Quercitrin and Quercitin, stated by Hlasiwetz to be present in tea, are described in Vol. III. Part I. page 341.

Boheic Acid, $C_7H_{10}O_6$, according to Rochleder (*Annalen*, lxiii. 202), exists to the extent of 0·1 to 0·2 per cent. in black tea. It is prepared by precipitating a boiling infusion of tea with acetate of lead, neutralising the filtered liquid with ammonia, suspending the washed precipitate in absolute alcohol, and decomposing it by sulphuretted hydrogen. The filtrate is evaporated to dryness *in vacuo*, and the residual boheic acid purified by resolution in water, &c. It is a yellow resinous body, melting at 100° to a tenacious manner, and decomposed on exposure to air. It is extremely soluble in water and alcohol, and giving a brown coloration but no precipitate with ferric chloride. The salts are mostly insoluble and amorphous.

[2] Eder's figures for mineral matters soluble in water are considerably lower than any other observer, and his proportion of insoluble matters is in excess and of soluble in deficiency of those usually recorded. His tannin, which was

The following analyses by Y. Kozai (*Bulletin*, No. 7, Imperial College of Agriculture, Japan) have a special value owing to the author's knowledge of tea manufacture. Special precautions were taken in sampling the leaves to ensure strictly parallel specimens being taken. The figures refer to the moisture-free leaves in each case :—

	Unprepared Leaves.	Green Tea.	Black Tea.
Caffeine or theine,	3·30	3·20	3·30
Ether-extract,	6·49	5·52	5·82
Hot-water extract,	50·97	53·74	47·23
Tannin (as gallotannic acid),	12·91	10·64	4·89
Other nitrogen-free extract,	27·86	31·43	35·39
Crude protein,	37·33	37·43	38·90
Crude fibre,	10·44	10·06	10·07
Ash,	4·97	4·92	4·93
Albuminoid nitrogen,	4·11	3·94	4·11
Caffeine nitrogen,	0·96	0·93	0·96
Amido-nitrogen,	0·91	1·13	1·16
Total nitrogen,	5·97	5·99	6·22

The proportion of ash found by Kozai is remarkably low, but it seems not impossible that this is characteristic of Japanese teas, since some analyses by J. Takayama (*Chem. News*, l. 299) show the same peculiarity.

An analysis of the so-called "flower of tea," consisting of the hairs of the leaf-buds of the tea-plant, has been published by T. B. Groves (*Year-Book Pharm.*, 1876, page 610).

James Bell (*Foods*, i. 6) gives the following figures as illustrating the composition of fair representatives of black and green teas of commerce :[1]—

determined by precipitation with cupric acetate, is unusually low. Of the extract, from 15 to 16 per cent. was precipitable by strong alcohol. A nitrogen determination on the precipitate gave a result corresponding to about 12 per cent. of albuminous matters, and the difference was regarded as gummy substances. The chlorophyll, wax, and resin were extracted by ether from the insoluble matter, after drying, and the residual cellulose purified by treatment with nitric acid, potash, and alcohol.

[1] It is evident that in these analyses some constituent was determined by difference, but it is not stated which. Nor does Bell state the method used for determining the tannin, the figures for which are highly improbable, while other of his descriptions are incomplete or obscure.

	Congou (Black).	Young Hyson (Green).
Moisture,	8·20	5·96
Caffeine,	3·24	2·33
Albumin, insoluble,	17·20	16·83
Albumin, soluble,	·70	·80
Extractive by alcohol, containing nitrogenous matter,	6·79	7·05
Dextrin or gum,	...	·50
Pectin and pectic acid,	2·60	3·22
Tannin,	16·40	27·14
Chlorophyll and resin,	4·60	4·20
Cellulose and insoluble colouring matter,	34·00	25·90
Ash,	6·27	6·07
	100·00	100·00

The following figures are given by J. P. Battershall (*Food Adulteration*, page 28) as the results of the analysis by American chemists of samples representing 2414 packages of Indian tea, a class remarkable for their general strength, high quality, and freedom from adulteration:—

	Minimum.	Maximum.	Average.
Moisture,	5·83 per cent.	6·32 per cent.	5·94 per cent.
Insoluble leaf,	47·12 ,,	55·87 ,,	51·91 ,,
Extract,	37·80 ,,	40·35 ,,	38·84 ,,
Tannin,	13·04 ,,	18·87 ,,	15·32 ,,
Caffeine or theine,	1·88 ,,	3·24 ,,	2·74 ,,
Ash :—Total,	5·05 ,,	6·02 ,,	5·61 ,,
Soluble in water,	3·12 ,,	4·28 ,,	3·52 ,,
Insoluble in acid,	0·12 ,,	0·30 ,,	0·18 ,,

The following figures, obtained by C. M. Caines in the author's laboratory, are interesting as indicating the character of the first parcel of *Natal tea* ever imported into England :[1]—Moisture, 8·36

[1] Natal tea must not be mistaken for the so-called "Cape tea" and "Bush tea," consisting of the dried leaves and twigs of certain species of *Cyclopia*. According to H. G. Greenish (*Pharm. Jour.*, [3], xi. 549, 569, 832), Cape tea is destitute of caffeine or other alkaloid, but contains a

per cent.; insoluble matter, 51·96; hot-water extract (complete), 39·68; tannin by $Pb\bar{A}_2$, 8·33; tannin by $Cu\bar{A}_2$, 8·50; caffeine by $Pb\bar{A}_2$ and chloroform, 2·85; total ash, 6·14; soluble ash, 3·56; alkalinity (K_2O) of soluble ash, 1·15 per cent.

The Moisture contained in commercial tea varies within somewhat wide limits (4·2 to 10·8 per cent.); but the range is far less when teas of the same class are compared. Thus G. W. Wigner (*Pharm. Jour.*, [3], vi. 361) found that hyson and gunpowders, both of which are highly-dried teas, contained the smallest proportions of moisture (4·84 to 6·55 per cent.), and, after drying at 100°, absorbed from 6·04 to 6·98 per cent. of water on exposure to air. Congou teas showed in their original condition an average of 8·50 per cent. of moisture, and never wholly regained their original weight on exposure to air after drying at 100°. The average proportion of moisture in commercial tea is about 7·7 per cent., and the usual range between 7 and 9 per cent.

Caffeine or Theine. The proportion of alkaloid present in tea varies considerably, the general range being from 3·0 to 4·0 per cent.; but the experiments of Paul and Cownley (page 492) show that in Indian and Ceylon tea the proportion is more frequently above 4 per cent. than below that figure; and in a special sample of Himalayan tea, Zöller found as much as 4·94 per cent. of caffeine, in addition to a small proportion of what was apparently theobromine. Unfortunately, by far the greater number of published determinations of caffeine are quite unreliable (see page 484), and, indeed, the low figures recorded suffice to indicate their inaccuracy; and hence any deductions as to the relation of the quality of tea to the proportion of alkaloid present must be received with great caution. The proportion of caffeine is not generally considered to have any direct relation to the commercial value of the tea, and the tea-taster takes no cognisance of it. The results of J. F. Geisler (page 506) tend to show that the proportion of caffeine which passes into the infusion has a relation to the quality of the tea, the superior qualities giving up their alkaloid to water more perfectly than the inferior; but as the whole of Geisler's figures for caffeine (1·15 to 3·50 per cent.) are probably below the truth, too

glucosidal body called cyclopin, $C_{25}H_{28}O_{13}$, similar to cinchona-novatannic acid, and yielding, when boiled with dilute acid, glucose, and a substance of the formula $C_{19}H_{22}O_{10}$, closely resembling cinchona-nova-red. Greenish also found a crystalline substance exhibiting a green fluorescence in alkaline solutions, and probably identical with the cyclopic acid previously described by A. H. Church (*Chem. News*, xxii. 2); and likewise a third substance analogous to cyclopin, and apparently an oxidation-product of that body. Cape tea yielded the author 30 per cent. of extract, and on ignition left 3·7 per cent. of an ash containing manganese.

much stress must not be laid on this conclusion;[1] and the same remark is applicable to the proposition of P. Dvorkovitch, that the higher the proportion of alkaloid bears to that of the tannin and fermentation-products, the more valuable is the tea. This varied from 16·0 : 84 to 24·5 : 75·5, the percentage of alkaloid in the tea itself ranging from 2·14 to 3·45 per cent.

CHLOROPHYLL. When either green or black tea is boiled with alcohol or chloroform a solution of a more or less grass-green colour is obtained, owing to the extraction of chlorophyll. E. B. Kenrick states that cheap black teas yield less chlorophyll than the better kinds, and believes that a distinction of practical value might probably be based on a colorimetric determination.

EXTRACT. By the term "extract," when used in reference to tea analysis, is understood the sum of the soluble matters extracted from the leaf by boiling water. It includes caffeine, tannin, albuminous matters, gum, dextrin, colouring matter, mineral matter, &c., besides other less important constituents, such as gallic acid, boheic acid, oxalic acid, and quercetin, which substances are present in comparative small quantity, if at all.

The proportion of *extractive matter* yielded necessarily varies with the method used to exhaust the tea, and is, of course, higher when the tea is powdered and the treatment with water long continued and carried to an extreme than when the whole leaves are used and the tea simply infused in boiling water. The latter method commends itself when the object is to study the character of the infusion likely to be yielded in practice, while the former plan gives more information when the objection is the detection of adulteration.

An interesting comparison of the results of the two methods has been made by J. F. Geisler, who has published an extensive series of analyses of teas obtained direct from American importers and wholesale houses (*American Grocer*, Oct. 23, 1884; *Analyst*, ix. 220; Prescott's *Organic Analysis*, page 505 *et seq.*). The following table by Geisler shows the proportions of extract, tannin, caffeine, and ash which passed into solution when various representative commercial teas were infused under precisely the same conditions by pouring on the leaves 100 times their weight of boiling distilled water, and allowing the liquor to "draw" for ten minutes. The ratio which the dissolved constituent bore to the total is also given.

[1] In a private communication to the author, Mr Geisler states that the caffeine was determined by mixing the concentrated decoction with magnesia and sand, and exhausting the dry mixture with chloroform (compare page 486).

Kind of Tea.	Wholesale Price per lb. in Cents.	Extract.		Tannin.[2]		Caffeine.	Ash.	
		Infusion.	Ratio to Total.	Infusion.	Ratio to Total.	Infusion.	Infusion.	Ratio to Total.
Fine Ceylon Pekoe tips,[1] .	...	33·25	76·6	17·19	75·3	2·44	3·44	91·0
Assam, ...	23⅛	29·15	73·5	11·48	60·8	3·30	3·80	70·0
Assam, ...	22⅙	28·57	72·0	9·50	58·4	2·75	4·40	79·5
Finest Moyune Gunpowder,	75	37·32	73·2	16·79	87·8	2·95	4·00	55·8
Common Moyune Gunpowder, . . .	18	28·07	79·4	9·26	77·7	1·67	4·02	66·1
Japan Basket-fired, . .	...	31·75	75·6	11·23	74·5	2·17	4·27	80·8
Japan Pan-fired, . .	...	34·37	79·6	13·41	94·4	2·07	3·67	63·6
Choicest Formosa Oolong, .	65	33·62	75·9	12·91	75·6	2·50	4·00	71·3
Choicest Formosa Oolong, .	53	33·30	73·7	13·75	68·5	2·42	3·97	66·5
Superior Formosa Oolong, .	30	29·00	68·6	9·63	59·6	2·12	3·66	62·3
Medium Amoy Oolong, .	24	27·40	60·9	10·12	56·0	1·92	3·72	68·5
Medium Amoy Oolong, .	21⅓	24·50	60·5	7·53	55·6	1·70	3·25	58·9
Choicest Moning Congou, .	45	24·25	70·6	5·46	41·7	2·87	4·13	73·7
Superior Moning Congou, .	27	21·55	57·8	4·44	32·0	2·77	3·70	63·5
Medium Moning Congou, .	19⅕	21·02	68·6	5·55	45·2	2·33	3·22	58·3
Good Common Kaisow Congou, . . .	17¼	23·25	64·1	4·05	38·5	2·35	3·30	59·9
Common Moning Congou,[3] .	15½	19·50	72·2	4·50	52·9	1·95	2·88	46·8

[1] *Jour. American Chem. Soc.*, xiii., No. 8.

[2] The determinations of tannin were made by the Löwenthal method, except in a few nstances in which the cupric acetate method was employed.

[3] This sample is considered by Geisler to have been adulterated, though its appearance did not indicate any admixture with exhausted leaves.—(Private Communication to Author.)

A comparison of these figures shows that, as a rule, the finer teas yield to hot water larger proportions of extract, caffeine, and ash than the inferior qualities. On an average, the ash of the extract exceeds by 0·62 per cent. the "soluble ash" obtained by treating the ash of the entire tea with water. The proportion of tannin rises and falls with that of the extract, and the ratio which the dissolved extract and tannin bear to the total has a notable relation to the price of the tea.

By the same method of 10 minutes infusion in boiling-hot water, E. B. Kenrick (*Bulletin* No. 24, Laboratory of Inland Revenue Department, Canada) obtained the following average results from commercial samples of tea:—

Description of Teas.	No. of Samples.	Aqueous Extract.	Tannin Dissolved.	Caffeine Dissolved.	Ratio of Aq. Extract to Tannin.
Congou, . . .	10	23·37	5·18	2·65	4·51
Assam, . . .	3	38·53	7·49	2·98	3·81
Ceylon, . . .	2	27·45	7·85	2·68	3·50
Unclassed Black, .	13	23·76	5·40	2·82	4·40
Japan, . . .	18	30·07	9·38	2·45	3·20
Gunpowder, . .	2	28·55	8·00	2·39	3·57
Young Hyson, . .	5	34·22	10·98	2·52	3·12

From these figures it appears that congou teas yield less extract than green and Japan teas, while Assam and Ceylon teas yield intermediate results. Not only do the Japan and green teas yield more soluble tannin than the black, but the proportion of tannin to the whole extract is greater in the former kinds. On the other hand, the black teas appear to yield more soluble caffeine than the Japan and green teas.

The following figures by Geisler show the influence of the time allowed for infusion upon the proportion of the constituents dissolved, and the difference in the result caused by substituting New York water (Croton River, of 4·96 degrees hardness per 100,000) for distilled water. In each case the tea used was the finest Formosa Oolong, and it was infused in 100 parts of boiling water:—

	Distilled Water.				Croton Water.	
	3 min.	5 min.	10 min.	1 hour.	5 min.	10 min.
Total extract,	25·97	28·37	30·87	33·75	27·47	30·25
Ash,	3·72	3·80	4·17	4·33	3·62	4·13
Extract *minus* ash,	22·25	24·50	26·70	29·42	23·85	26·12
Tannin,	9·75	11·23	13·46	14·94	10·18	10·60
Caffeine,	1·95	2·65	2·75	2·85	2·02	2·82
Alkalinity of infusion-ash (= K_2O),	1·03	1·08	1·22	1·28	1·08	1·15

From these results it appears that infusion in distilled water for 3 minutes is insufficient, but in 5 minutes practically as good a result is obtained as in a longer time, without so much astringent matter being extracted. When Croton water is used, 10 minutes gives a materially better result, so far as caffeine and extract are concerned, while the proportion of tannin is not increased in the same proportion. In all these experiments the volatile oil is left out of consideration, though it is to this constituent that the flavour and aroma of the tea is due, and on these characters the commercial value of the tea materially depends. The tannin and extractive matter impart astringency, strength, and body to the infusion. Caffeine, being almost tasteless, is not taken into account by tea-tasters, though physiologically it is the most important constituent of tea.

In tasting tea, it is usual to infuse the weight of a sixpenny piece (43 grains) of the sample in 3½ fluid ounces of boiling water, and to pour off the infusion after standing from 3 to 5 minutes, according to the practice of the taster. The infusion is not

swallowed, and, of course, no sugar or milk is added. In the process of manufacture, the different sized leaves are separated by sifting, and thus broken leaves and dust are obtained, which, though yielding a strong infusion, will be sold at a lower rate. Broken or powdered tea loses its aroma more rapidly than whole-leaf tea. Hence, in judging of the commercial value of a tea, the appearance of the leaf and extent to which it is damaged are taken into account as well as the characters of the infusion. The infusion is judged by its strength or astringency, its flavour, its colour, and its odour. The strength and flavour are dependent on the age, and consequently the size of the leaf, and the time the tea has been kept since its manufacture. A chemical analysis will indicate the strength, but not the flavour of the infusion, and hence is of little use in the valuation of high-priced teas; but as in medium and low-priced teas the strength is of as great or more importance than the flavour, a chemical analysis will, in such cases, go far to indicate the commercial value of the tea. The opinion formed of a tea by a professional taster is sometimes very different from that to which a chemical examination would lead.[1]

It is comparatively unusual for unmixed tea of any kind to be sold retail. Blending of several kinds is very generally practised, and when conducted judiciously materially improves the character of the tea.

[1] In 1874, the author submitted to two tea-tasters of considerable experience a series of samples which he had specially prepared to test their ability to recognise adulterations of tea by the taste. The following were the opinions expressed:—

Nature of Sample.	A's Opinion.	B's Opinion.
No. 1. 70 per cent. of No. 2 and 30 per cent. exhausted and redried leaves.	Tasted "washed-out;" no doubt from presence of exhausted leaves.	Very poor; contained many exhausted leaves; ranked *fifth*.
No. 2. Genuine black tea of fair quality.	Genuine.	Passed pure; ranked *first*.
No. 3. No. 2 somewhat crushed.	Mixed with exhausted leaves.	Would have been the best, but lacks strength, and is therefore suggestive of exhausted leaves. Ranked *third*.
No. 4. 80 per cent. of No. 2 and 20 per cent. of exhausted leaves, to which a little Na_2CO_3 was added while redrying.	Genuine; better tea than No. 3.	Not pure, but very slightly adulterated with exhausted leaves. Ranked *fourth*.
No. 5. 80 per cent. of No. 2, 20 per cent of exhausted leaves, and a little catechu.	A washed-out tea to which some astringent matter had been added.	Passed pure, and ranked *second*.

ADULTERATIONS OF TEA.

Before the passing of the Adulteration of Food Act of 1872, tea was subject to adulterations of the grossest kind,[1] most of which were practised prior to importation. By the Sale of Food and Drugs Act of 1875, provision was made for the examination of tea by the Custom House, and the exportation or destruction of very bad parcels.[2] Hence the tea now sold in the United Kingdom is rarely adulterated in the gross manner which was formerly common.[3]

The adulterants of tea may be conveniently arranged under the following four heads:—1. Mineral additions used for increasing weight or bulk; such as sand, magnetic iron ore, brass filings. 2. Organic additions used for increasing weight or bulk; such as previously infused leaves, and leaves other than those of the tea plant, as slow, elder, willow, &c. 3. Adulterants used for imparting fictitious strength, by increasing the astringency or deepening the colour of the infusion; as catechu, sodium carbonate, borax. 4. Facings and colouring materials; as steatite, prussian blue, indigo, turmeric, graphite, &c.

The practice of facing tea, formerly very common, is now confined to certain kinds of green tea, especially gunpowder, and the

[1] By section 5 of 11 George I. cap. 30, the adulteration of tea by terra japonica (catechu), leaves other than leaves of tea, or any other ingredients whatever, was punishable by forfeiture and a fine of £100. By section 11 of 4 George II. cap. 14, a penalty of £10 was imposed for the sale of every pound of tea which was mixed, coloured, stained, or dyed with terra japonica, sugar, molasses, clay, logwood, or with any other ingredients or materials whatsoever.

[2] On May 9, 1891, W. Cobden Samuel, the chief chemist in the Custom House Laboratory, reported that 437 samples had been analysed during the year 1890, viz.:—84 samples green faced tea; 10 green not-faced tea; 96 green caper tea; 154 black congou tea; 64 black dust tea; and 29 samples of siftings. Of these, 384 samples were found on analysis to be satisfactory. Of the remaining 53 samples, representing 516 packages of doubtful and unsound teas, 1 sample, representing 5 packages, was admitted to home consumption; 41 samples, representing 301 packages, were restricted to exportation, owing to the presence of exhausted leaves, damage, or other causes within the Act; 8 samples, representing 139 packages, were refused admission, as unfit for human food; and 3 samples, representing 71 packages, were on analysis found to be teas that had previously been imported, and ordered to be exported. They were this year reimported and relabelled as new season's teas. This fact, with the analysis, was reported to the Board of Customs, and the whole of the parcel of 71 packages was ordered to be seized under the Merchandise Marks Act.

[3] This statement does not apply to all countries. As recently as 1888, Wenda and Wiorogorski described various adulterations they had met with in tea sold in Warsaw. Bukowski and Aleksandrow in the same year found as much as 40 per cent. of ash in tea, and a considerable proportion of brass-filings in one sample.

mineral additions for increasing weight or bulk no longer include (so far as the United Kingdom is concerned) considerable proportions of magnetic iron ore, &c., as was formerly the case.

For the detection of *mineral adulterants*, and to obtain certain other knowledge, the tea should be ignited, and the proportions of ash soluble in water and acid determined. In practice this is best effected by igniting 5 grammes of the tea, in its ordinary commercial condition, in platinum, at as low a temperature as possible. When the carbon is burnt off, the ash will have a distinct green colour, owing to the formation of manganate. The ash is weighed and boiled with water, the solution filtered, and the residue washed, ignited, moistened with ammonium carbonate, very gently ignited, and weighed. The difference between the weight now found and that of the *total ash* gives that of the *ash soluble in water*.[1] The *insoluble ash* is next boiled with strong hydrochloric acid, the solution diluted with hot water, filtered, and the *insoluble residue* washed, ignited, and weighed. It consists of extraneous siliceous matter, such as sand, fragments of quartz, &c., and insoluble silicates, such as steatite from the facing of gunpowder tea. If titanic iron sand be present, some of it will almost certainly remain undissolved, and present the appearance of jet-black magnetic particles.[2]

The solution of the ash soluble in water should be titrated with

[1] If preferred, the weight of the soluble ash can be ascertained directly, by evaporating the solution and weighing the residue.

[2] The adulteration of tea with magnetic matter, formerly (in the experience of the author) very common, is now apparently nearly obsolete, a clear proof that the mineral admixtures were not due to accidental causes. Magnetic matter is best detected by reducing 10 grammes of the tea to powder and spreading it in a thin layer on a sheet of smooth paper. A magnet or electro-magnet is then applied to the under-side of the paper and moved laterally, with its poles in contact with the paper. Any magnetic matter may thus be readily drawn out and separated from the tea. It is next boiled with water for a few minutes to detach adherent organic particles, and the water decanted. The residue is then dried and weighed, and examined under the microscope as an opaque object. If it consists of magnetic oxide or titanate of iron, crystalline facets will probably be apparent, the bulk of the object having a jet-black colour. Metallic iron would be distinguished from the foregoing ferruginous minerals by its solubility in moderately strong nitric acid (sp. gr. 1·2) with evolution of red fumes, and by its precipitating metallic copper from a warm and slightly acidulated solution of cupric sulphate.

The weighing of the matter actually extracted by a magnet is far more satisfactory than the estimation of the iron existing in the tea. Tea naturally contains a small proportion of iron, but it only amounts to about 3 per cent. of the weight of the ash, or about 0·18 per cent. of the entire tea. Of course the iron in this form is not affected by a magnet, the use of which has the

methyl-orange or litmus and standard acid, the volume used being calculated to its equivalent of potassium oxide (1 c.c. of $\frac{N}{10}$ acid $= 0{\cdot}00471$ gramme of K_2O).

The analyses of a very large number of teas show that the proportion of soluble ash and its alkalinity vary with the age of the leaves, the figures yielded being highest with young leaves and teas of high quality. The total ash of absolutely pure tea rarely, if ever, exceeds 6 per cent., but some licence must be allowed in dealing with commercial samples. Hence in 1874, the Society of Public Analysts suggested 8 per cent. as the maximum limit of total ash allowable in tea, of which not less than 3 per cent. should be soluble in water. These figures refer to tea previously dried at 100°, and as the proportion of water usually lies between 7 and 8 per cent., the corresponding limits for tea in its ordinary commercial condition will be 7·40 and 2·77 per cent. respectively.

Somewhat more recently (1875), G. W. Wigner (*Pharm. Jour.*, [3], vi. 262, 281) obtained the following average results by the analysis of sixty-seven samples of commercial tea taken from the original chests. The samples embraced forty-one of ordinary character, eighteen special teas of high price, and nine samples of caper. Wigner regarded and described these last as "genuine," and they were clearly free from any large proportion of mineral adulterants, but the author strongly questions whether any specimen whatever of caper tea really deserves the description of "genuine."

	Results of Analysis of Ash.			
	Total.	Siliceous Matter.	Soluble in Water.	Alkalinity as K_2O.
Samples in Commercial State—				
Maximum,	7·02	1·67	3·88	1·96
Minimum,	5·17	0·04	2·64	1·08
Average,	5·78	0·46	3·15	1·45
Samples after drying at 100° C.—				
Maximum,	7·42	1·76	4·16	2·11
Minimum,	5·57	0·04	2·94	1·26
Average,	6·33	0·50	3·45	1·54

advantage of extracting the iron in the form in which it actually exists, and production in court if necessary.

In 1873 and 1874 the author frequently found from 5 to 8 per cent. of magnetic matter in caper tea, and at that time the use of the magnet for its detection was well known to, and habitually practised by, the trade.

The ash of these sixty-seven samples of tea had the following average composition :—

	Including Silica, &c.	Exclusive of Silica, &c.
Siliceous matter,	7·96 per cent.	... per cent.
Soluble in acid,	37·54 ,,	40·79 ,,
Soluble in water,	54·50 ,,	59·21 ,,
	100·00 per cent.	100·00 per cent.
Alkalinity of soluble ash, as K_2O,	25·09 per cent.	27·26 per cent.

James Bell (*Foods*, i. 29, 31) has published figures agreeing with those of Wigner. The proportion of soluble ash in genuine teas analysed by Bell ranged from 2·8 to 4·2 per cent. (calculated on the moisture-free tea), the proportion being usually between 3·2 and 3·6 per cent. In one instance only did the soluble ash fall below 3 per cent., and in that case the deficiency was very trifling, the proportion being 2·97 per cent. The alkalinity of the soluble ash of the teas examined by Bell ranged from 1·30 to 1·91 per cent. of K_2O. In only one case did the total ash reach 8 per cent., while the insoluble siliceous matter exceeded 1 per cent. in a few instances only. Bell's results are fairly in accordance with the wide experience of the author (see *Chem. News*, xxix. 167, 189, 221).[1]

[1] The following results of partial analyses of average samples of commercial black teas, as ordinarily imported, have been communicated to the author by M. J. Sheridan, Assistant Chemist in H.M. Customs Laboratory. The figures refer to the undried tea :—

Description of Tea.	Ash.			Extract; on Whole Leaves.
	Total.	Soluble in Water.	Siliceous Matter.	
INDIAN :—				
Orange Pekoe,	5·40	3·20	0·45	40·49
Assam Pekoe,	6·10	3·30	0·90	39·32
Souchong,	5·70	3·15	0·60	39·44
Pekoe Souchong,	5·75	3·25	0·70	38·78
CEYLON :—				
Broken Orange Pekoe,	5·50	3·20	0·20	42·90
Ceylon Pekoe,	5·40	3·35	0·25	38·24
Souchong,	5·60	3·40	0·30	37·98
JAPAN :—				
Siftings,	6·12	3·15	0·95	29·80
JAVA :—				
Congou,	5·60	3·05	0·50	34·60
Congou,	7·65	3·75	1·05	30·72
CHINA :—				
Kaisow Congou,	5·70	3·25	0·50	32·95
Common Congou,	5·85	2·95	1·00	31·71
Souchong,	5·00	3·05	0·65	33·57
Oolong,	5·65	3·20	0·70	34·10
Flowery Pekoe,	5·45	3·05	0·55	35·70
PORT NATAL :—				
Congou,	5·65	3·10	0·45	34·80

In certain cases a high soluble ash does not indicate a high quality of tea. This happens when the ash contains a notable proportion of sodium chloride, owing to the tea having been damaged by sea-water and redried. The ash of pure tea contains only a trifling proportion of sodium, less than 2 per cent., and the chlorine does not exceed 1·1 per cent., equivalent to about 1·8 of sodium chloride, representing 0·108 per cent. of the weight of the tea. Wigner (*Pharm. Jour.*, [3], vi. 403) found 3·08 per cent. of sodium chloride in tea which had been a fortnight under sea-water and completely soaked, and 0·17 and 0·23 in samples which had been slightly moistened.

Previously infused or exhausted leaves are among the adulterations of tea most difficult to detect, especially when present only in moderate proportion. The sophistication of tea in this manner was formerly extensively practised in England, the exhausted leaves being treated with gum or other matters, and rolled and redried so as to resemble genuine tea.[1]

The treatment of tea with hot water necessarily results in the removal of certain of the ash-constituents, especially the potassium salts of organic acids. Hence the exhausted leaves will contain a smaller proportion of total ash, and especially of ash soluble in water. The extent of the change produced by infusion will, of course, depend on the perfection of the exhaustion. The author found in a mixture of infused leaves from various teas 4·30 of total ash, of which 0·52 per cent. was soluble in water. James Bell (*Analysis and Adulteration of Foods*, i. 29) gives the following figures obtained by the analysis of the ash of tea-leaves which had been infused in the ordinary way for domestic use, and afterwards redried at 100°:—

Description of Tea.	Ash of Sample.			
	Total.	Siliceous Matters.	Soluble in Water.	Alkalinity, as K_2O.
Congou, . . .	3·92	0·41	0·54	0·11
Moning, . . .	4·53	0·95	0·85	0·28
Orange Pekoe, . .	3·77	0·57	0·68	0·18
Hyson, . . .	5·56	1·40	0·76	0·21
Souchong, . . .	4·12	0·70	0·81	0·19

[1] Though less extensively carried on than formerly, the practice of redrying infused tea-leaves is not obsolete. The infused tea-leaves from the various bread and kindred shops, now so numerous in London, are regularly

The total ash of the foregoing samples averages 4·38, and the soluble ash 0·73 per cent.

Exhausted tea-leaves are also indicated by the deficient extract (and consequently high insoluble matter) and low proportion of tannin.[1] As already stated, the yield of extract depends materially on the condition of the tea, more complete extraction of the soluble matters being effected when the powdered tea is used than when the exhaustion is effected on the leaves in their commercial condition. For the purpose of detecting adulteration, the powdered tea should always be used, or the results will not be fairly comparable.

The determination of the total extract and insoluble matter of tea is best effected by boiling 2 grammes of the tea in a state of powder with 100 c.c. of water for one hour. The liquid is filtered while hot, the residue boiled again with 50 c.c. of water, and the process repeated as long as colouring matter continues to be extracted, the liquid being poured through the filter previously used.[2] After cooling, the decoction is made up to 250 c.c., or other convenient measure, and an aliquot part (one-fifth) evaporated to dryness for the determination of the extract. The filter and its contents should be dried at 100°, and the insoluble matter detached and weighed. Very constant results are thus obtainable.

The minimum proportion of extract yielded by genuine tea exhausted in a state of powder was fixed by the Society of Public Analysts in 1874 at 30 per cent. Assuming the presence of 7·5 per cent. of moisture, this leaves 62 per cent. for the maximum proportion of insoluble matter. This figure covers almost all legitimate variations in tea, and is considerably in excess of the proportion yielded by green tea, the insoluble matter from which averages 42 per cent., while in black teas the average is only about 50 per

bought up and redried; and the leaves of the tea infused by tea-tasters are systematically preserved and sold for the same purpose.

[1] J. M. Eder obtained the following figures by the analysis of teas adulterated with exhausted leaves purchased in small shops in the suburbs of Vienna :—

	Tannin (by $Cu\bar{A}_2$).	Extract.	Total Ash.	Soluble Ash.
Russian tea, . .	6·60	18·4	4·76	0·85
Bloom tea, . .	4·91	15·3	3·34	0·64
Bloom tea, . .	5·13	14·6	4·51	0·90

[2] The decoction of some teas filters very slowly, and it is necessary to strain the liquid through fine muslin instead of filtering it through paper.

cent. In the case of old-leaf Congou teas containing much stalk, and which have been stored for some time, the extract may occasionally fall to 30 per cent., corresponding to 62½ per cent. of insoluble matter. In judging a tea by the proportion of extract or insoluble matter, it is very desirable, when possible, to take into account the character of the sample. Thus young leaves (which are to some extent indicated by their size) yield a notably higher extract than fully grown or old leaves, or specimens containing a considerable proportion of stalk.

G. W. Wigner has recorded the proportions of extract yielded by a sample of tea in powder when boiled with different quantities of water. In each case the tea was boiled with the water under a reflux condenser for one hour, the decoction cooled, filtered, and evaporated to dryness.

A.	1 part of tea in 200 parts of water yielded	34·10		per cent. of extract.
B.	,, ,, 100 ,, ,,	30·55		,, ,,
C.	,, ,, 50 ,, ,,	27·55		,, ,,
D.	,, ,, 20 ,, ,,	22·90	36·67 (D–G)	,,
E.	Exhausted leaves from expt. D in 20 parts water, ...	8·17		
F.	,, ,, E ,,	3·75		
G.	,, ,, F ,,	1.75		

Even after four boilings with 20 parts of water, the tea was not completely exhausted. Hence Wigner preferred to determine the extract by boiling the powdered tea once, for one hour, with 100 parts of water, instead of repeatedly exhausting with smaller quantities. Operating in this manner he obtained proportions of extract ranging from 26·15 to 44·85 per cent., the average being 35·70 per cent., containing 4·63 of ash.[1]

The determination of tannin in tea affords valuable information respecting the probable presence of *previously infused leaves* or *extraneous tannin matters*, such as catechu. This is best effected in the aqueous decoction obtained by exhausting the sample with boiling water, as required for the determination of the extract.

The tannin may be estimated by H. R. Procter's modification of Löwenthal's process, as described in Vol. III. Part I. page 110. A volume of the above decoction, corresponding to 0·04 gramme of tea, may be taken for the original titration with permanganate; and of the decoction deprived of tannin a volume correspond-

[1] The ash of the soluble extract of tea always exceeds by a considerable amount the proportion of tea-ash soluble in water, doubtless owing to the presence in tea of soluble salts of calcium and magnesium with organic acids, which salts on ignition are converted into calcium carbonate and magnesia, and thus become insoluble in water.

ing to 0·080 gramme of tea. The tannin of tea is stated by some chemists to be gallotannic acid, and by others to be identical with that of oak-bark. The reduction-equivalent of the latter is almost identical with that of crystallised oxalic acid, so that the weight of this substance corresponding to the volume of permanganate decolorised gives without calculation that of the tannin present.

The process of fermentation to which black tea has been subjected undoubtedly causes modification of the tannin, with formation of dark-coloured insoluble matter. The author found that a tincture of green tea precipitated tincture of ferric chloride bluish black, like nut-galls, while the tincture of black tea gave a green colour with iron, just as catechu does.

A modification of the permanganate process, which appears to possess some advantages for the examination of tea, has been described by P. Dvorkovitch (*Ber.*, xxiv. 1945; *Jour. Chem. Soc.*, lx. 1302), who aims not only in estimating the tannin but also the proportion of *fermentation-products* formed in the process of fermentation to which black tea has been subjected. For this purpose he treats 10 grammes of finely-powdered tea with three successive quantities of 200 c.c. of boiling water, five minutes being allowed for each digestion. The residue is then boiled twice with 200 c.c. of water, or until the last extract is almost, if not entirely, free from colour, when the decoction is diluted to 1 litre. Forty c.c. of this solution is then diluted to 500 c.c. with water, and treated with 25 c.c. of indigo-carmine solution[1] and 25 c.c. of dilute sulphuric acid (200 grammes of H_2SO_4 per litre). The liquid is then titrated with a standard solution of potassium permanganate (containing approximately 2·6 grammes per litre), and of such strength that 130 c.c. are equivalent to 100 c.c. of decinormal oxalic acid (6·3 grammes crystallised acid per litre). The mode of adding the permanganate is important, and Dvorkovitch recommends that in the titration of the indigo-carmine 18 c.c. should be added at the rate of 2 to 3 drops per second, and the remainder at the rate of 1 drop per second; and that, in the titration of the tea solution mixed with indigo-carmine, 23 c.c. of the permanganate should first be run in, the addition continued at the rate of 2 to 3 drops per second, and finally 1 drop per second added until the reaction is complete. If more than 38 c.c. be required, a small quantity of tea infusion should be used. To estimate the *fermentation-products*, 80 c.c. of the tea infusion is mixed with 20 c.c. of baryta-water (containing 4 grammes of baryta

[1] Prepared by mixing 50 grammes of pure indigo-carmine paste with water, adding 50 grammes of sulphuric acid and 1 litre of water, filtering, and diluting till 25 c.c. require 20 c.c. of the standard permanganate for oxidation.

per 100 c.c.), the liquid filtered, and 50 c.c. of the filtrate (representing 0·4 gramme of the tea) diluted with 500 c.c. of water, mixed with 25 c.c. of dilute sulphuric acid and 25 of the indigo-carmine solution, and titrated with permanganate. 18 c.c. should be run in first of all, then 2 or 3 drops per second added, and finally 1 drop per second till the end of the reaction. The volume of permanganate required, less that reduced by the indigo solution, represents that required for the oxidation of the fermentation-products of 0·4 gramme of tea. According to Dvorkovitch, the joint weight of tannin and fermentation-products is obtained by multiplying the weight of oxalic acid equivalent to the measure of permanganate required for their oxidation by 31·3, since 63 grammes of oxalic acid correspond, according to Dvorkovitch's experiments, to 31·3 grammes of tea-tannin (as compared to 62·3 of quercitannic acid!). Employing this process, he found from 8·84 to 10·55 per cent. of tannin, and from 0·90 to 1·88 of fermentation-products, in teas of the first crop of 1890; and he concludes that the higher the proportion of caffeine to the total amount of tannin and fermentation-products, the more valuable is the tea.

The Löwenthal process distinguishes the tannic acid from the small quantity of gallic acid also present in tea, but as the astringent character of the infusion is due to both these substances, a method which will estimate the total amount of astringent matter, without distinction of its nature, is in some respects preferable to a process that gives merely the amount of tannin, while ignoring the gallic acid. Such a process was devised by F. W. Fletcher and the author in 1874 (*Chem. News*, xxix. 169, 189), and was based on the precipitation of the tea infusion by lead acetate, and the use of an ammoniacal solution of potassium ferricyanide to indicate the complete precipitation of the astringent matters. In practice, 5 grammes of neutral acetate of lead should be dissolved in distilled water, and diluted to 1 litre, and the solution filtered after standing. The indicator is made by dissolving 0·050 gramme of pure potassium ferricyanide in 50 c.c. of water, and adding an equal bulk of strong ammonia solution. This reagent gives a deep red coloration with gallotannic acid, gallic acid, or an infusion of tea. One drop of the solution will detect 0·001 milligramme of tannin, or 0·001 gramme dissolved in 100 c.c. of water. In carrying out the process, three separate quantities of 10 c.c. each of the standard lead solution should be placed in beakers, and each quantity diluted to about 100 c.c. with boiling water. A decoction made from 2 grammes of powdered tea in 250 c.c. of water (the same as is used for determining the extract) is added from a burette, the first trial quantity receiving an addition of 12, the second 15, and the third

18 c.c.; or if green tea be under examination, 8, 10, and 12 c.c. may be preferably employed. Portions (1 c.c.) of these trial quantities are passed through small filters, and the filtrates tested with ammoniacal ferricyanide solution.

The approximate volume of tea decoction required is thus easily found, and after repeating the test nearly the requisite measure can be at once added. In this case about 1 c.c. of the liquid should be removed with a pipette, passed through a small filter, and drops of the filtrate allowed to fall on to spots of the indicating solution previously placed on a porcelain slab. If no pink coloration is observed, another small addition of the tea decoction is made, a few drops of the liquid filtered and tested as before, and this process repeated until a pink colour is observed. The greatest delicacy is obtained when the drops of filtered solution are allowed to fall directly on to the spots of the indicator, instead of observing the point of junction of the liquids.

The volume of tea solution it is necessary to add to 100 c.c. of pure water, in order that a drop may give a pink reaction with the indicator, should be subtracted from the total amount run from the burette.

The foregoing process is simple, and gives very concordant results; but the repeated filtrations requisite for the observation of the end-reaction are apt to be tedious. It is difficult to obtain pure tannin for setting the lead solution, and hence it is preferable to abandon the attempt and make pure lead acetate the starting-point. The author found that 10 c.c. of the lead solution would precipitate 0·010 gramme of the purest gallotannic acid he could obtain. Hence, if all the weights and measures above mentioned be adhered to, the number of c.c. of tea decoction required, divided into 125, will give the percentage of tannin and other precipitable matters in the sample. The proportion found in undried black tea by F. W. Fletcher and the author ranged from 8·5 to 11·6 per cent., with an average of 10 per cent. A sample of brown catechu tested by the lead process gave a result corresponding to the presence of 119 per cent. of tannin (*sic*). (See also page 491.)

Another simple method for the determination of tannin is that of J. M. Eder (*Dingl. Polyt. Jour.*, ccxxix. 81), which consists in precipitating the boiling decoction of 2 grammes of tea with excess of a 5 per cent. solution of cupric acetate. The precipitate is separated by filtration, washed, dried, and ignited. The resultant cupric oxide, CuO, can be moistened with nitric acid, re-ignited and weighed as such; or re-ignited with sulphur in a closed crucible, and thus converted into an equal weight of non-hygroscopic cuprous sulphide, Cu_2S. The weight obtained, multiplied by 1·305, gives that of the tannin precipitated. The method is said to give

results correct to within 0·2 to 0·3 per cent.; but any pectous bodies should be previously separated, if present in quantity, by precipitation with alcohol. By this method Eder found an average of about 10 per cent. of tannin in twenty-five samples of black tea, and 12 to 12½ in green and yellow tea. S. Janke, by the same process, found from 6·9 to 9·1 per cent. of tannin in black tea (eighteen samples), and 8·6 to 9·9 in green. Cupric acetate may be extemporised by mixing a solution of cupric sulphate with excess of sodium acetate.

C. M. Caines (page 491) obtained results by Eder's method closely agreeing with those yielded by the same samples with the lead process, and hence the proportion of gallic acid in tea is probably very insignificant.

In the case of caper and lie teas, the astringency is often very high, owing to an admixture of *extraneous tannin matters;* but the evidence of the presence of such additions afforded by the determination of the tannin of tea is, of course, merely inferential. Strong infusions of genuine tea, with the exception of some kinds from India, are generally quite clear, and do not become muddy on cooling. Tea adulterated with catechu gives an infusion which quickly becomes turbid on cooling. More direct proof of the presence of *catechu* may be afforded by the following test devised by the author, which, however, should always be applied to the suspected tea side by side with a genuine specimen :—One gramme of the pure tea and an equal weight of the suspected sample are infused in 100 c.c. of boiling water, and the strained liquid precipitated while boiling with a slight excess of neutral lead acetate. Twenty c.c. of the filtrate from pure tea (which should be colourless) when treated with a few drops of silver nitrate solution (avoiding excess), and cautiously heated, gives only a very slight greyish cloud or precipitate of reduced silver; but the same tea containing 2 per cent. of catechu (purposely added) gives a copious brownish precipitate, the liquid acquiring a distinctly yellowish tinge. With a somewhat larger proportion of catechu, the filtrate from the lead precipitate gives a bright green colour on adding one drop of dilute ferric chloride, while the solution of pure tea gives only a slight reddish colour due to the presence of acetate. On allowing this liquid to stand, the adulterated tea gives a precipitate of a greyish or olive-green colour, the pure tea undergoing no change.

These tests, which depend on the properties of catechuic acid, together with the excessive proportion of astringent matters (as shown by the lead process), render the detection of any considerable proportion of catechu tolerably certain; but a means of detecting small additions is still a desideratum.

Catechu is usually introduced in the forms of caper and lie tea, but appears to have been sometimes added in a separate state, to impart additional "roughness" or to cover the presence of exhausted leaves.

Caper is a name applied to tea which has been made up into small glossy granular masses by the aid of gum or starch. Some years ago the caper tea from the Canton district was invariably adulterated with sandy and magnetic matter, and often with catechu or other extraneous astringents, together with foreign leaves.[1] Notwithstanding the conviction of Wigner and some other authorities that genuine caper tea exists, the author believes it to be invariably a factitious article.

Lie tea is the name given to a fraudulent mixture consisting of sweepings and dust of tea and other leaves, mixed with clay, sand, iron ore, &c., and made into irregular masses by means of gum or starch. When put into hot water, lie tea disintegrates and falls to powder. The iodine test for starch may be applied after acidifying the cold liquid with sulphuric acid, and decolorising with permanganate. The ash of lie tea is sometimes as high as 30 to 40 per cent.

The insoluble matter and extract of lie and caper tea are very variable; but the former, exclusive of mineral matter, is usually considerably below the proportion yielded by genuine tea. The gum[2] in caper tea often amounts to 15 or 20 per cent., while the soluble ash is often less than 2 per cent.

The following figures show the results to be expected from the analysis of factitious tea :—

	A.	B.	C.
Observer,	J. Bell.	J. M. Eder.	A. B. Hill.
Description,	"Mahloo mixture."	Black tea.	Green tea.
Extract,	...	22·40	37·00
Tannin,	...	19·77 (Catechu detected)	Catechu detected.
Total Ash,	0·97	3·07	12·10
Magnetic and sandy matter,	4·31	...	6·00
Soluble Ash,	1·54	1·12	1·29
Alkalinity, as K_2O,	0·17	...	0·13

[1] At the present time (August 1892), Canton capers are frequently loaded with from 3 to 5 per cent. of sand, &c., but they rarely appear in the home market, being stopped by the Customs, or purposely imported for future exportation (M. J. Sheridan).

[2] The gum is determined by concentrating the aqueous decoction of the tea

The following analyses of samples of spurious tea, received from the U.S. Consuls at Canton and Nagasaki, are by J. P. Battershall (*Food Adulteration*, page 28). No. 1 consisted of partially exhausted and refired leaves known as "*ching suey*" (clear water), a name apparently referring to the character of the infusion. No. 2 was a sample of "lie-tea" made from wampan leaves. No. 3 was a mixture of 10 per cent. of green tea with 90 per cent. of lie-tea, sometimes sold as "Imperial" or "Gunpowder" tea. No. 4 was a sample of "scented caper," consisting of tea-dust made up into little shot-like pellets by means of "Congou paste" (boiled rice):—

	No. 1.	No. 2.	No. 3.	No. 4.
Insoluble leaf,	70·60	70·55	67·00	60·10
Extract (complete),	7·73	14·00	12·76	22·10
Gum,	10·67	7·30	11·00	11·40
Tannin,	3·13	8·01	14·50	15·64
Caffeine,	0·58	none	0·16	0·12
Ash:—Total,	8·62	8·90	7·95	12·58
Soluble in water,	0·64	1·86	3·00	3·84
Insoluble in acid,	3·92	3·18	1·88	6·60

Logwood is mentioned by Eder as an adulterant of tea. To detect it, he steeps the tea in cold water. If logwood be present, the resultant solution is changed to a bright green on adding a little sulphuric acid, and to blackish-blue by a solution of neutral chromate of potassium.

Facings and colouring materials were formerly almost invariably present in green tea,[1] the object being to impart a hue demanded by custom but not naturally possessed by the leaf. Colouring matters have been extensively employed for transforming black tea of low quality into superior green.

In the case of Roberts *v.* Egerton, heard before the Court of

almost to an extract, treating the residue with strong spirit, and filtering and washing with spirit. The precipitate is rinsed off the filter with hot water, and the solution evaporated to dryness at 100°. The residue is weighed, ignited, and the ash weighed. The loss is regarded as "gum," but is liable to be in excess of the truth from the presence of albuminous matters.

[1] It is a fact well known to the trade that for many years a certain firm of tea merchants used some method of removing the facing after the arrival of the tea in this country.

Queen's Bench in 1874, Mr Justice Blackburn decided that the facing of green tea with gypsum and prussian blue was an adulteration, because natural green tea could be obtained without such means.[1]

If a faced tea be examined under the microscope as an opaque object, the nature of the facing materials may often be recognised. On treating a faced tea with warm water, the colouring matters become detached, and the small portions rising to the surface may be floated on to a glass slide and at once examined under a microscope, while the bulk of the facing is obtained as a sediment when the strained liquid is allowed to stand.[2]

Foreign leaves in tea are legitimately present in small proportion (1 to 3 per cent.) to impart bouquet,[3] but larger admixtures can simply be regarded as due to adulteration. *Sloe, elder,* and *willow* leaves have been (formerly) met with in England as adulterants of tea.[4] Among the recently-found leaves added abroad, and stopped by the Customs, are those of *Chloranthus inconspicuus, Camellia sasanqua, Eurya Chinensis,* and *sloe*.[5] In the recognition of foreign

[1] The teas consumed by the Chinese and Japanese themselves are not faced. According to Y. Kozai the maximum proportion of facing in the green tea of Japan is about 0·4 per cent.

[2] This deposit often has a distinctly greenish colour from the presence of prussian blue or indigo. Indigo may be recognised by its behaviour with nitric acid. Prussian blue is best detected by warming the sediment with caustic alkali, filtering, strongly acidulating the filtrate with hydrochloric acid, filtering again if necessary, and testing the clear liquid for ferrocyanide with ferric chloride. On treating the sediment with the alkali it is sure to turn brown, but this change must not be regarded as an indication of the presence of prussian blue. The residue left after treatment with the caustic alkali should be treated with hydrochloric acid, when the insoluble portion will usually consist of *steatite* or other *magnesian silicate,* the use of which gives the tea a peculiar smooth appearance and slippery feel. *Calcium sulphate* is often employed for facing tea. Caper tea is often glazed with *graphite. Turmeric* has been detected by some observers, but in the experience of the author the yellow colouring matter has generally been of a ferruginous nature.

[3] As a rule, the odoriferous leaves are not allowed to remain in the tea, but having imparted their characteristic fragrance to the tea are removed previously to packing.

[4] From the result of a parliamentary inquiry held in 1835, it appeared that upwards of four million pounds of factitious tea were annually prepared in this country from sloe leaves, and used to adulterate China tea. Up till within a few years of that date this illicit practice was carried on secretly, but subsequently a patent was obtained for the preparation of British leaves as a substitute for tea, and an extensive manufactory was established for this purpose. The industry was ultimately suppressed, and a large quantity of the product burned.

[5] In 1888 Wenda and Wiorogorski found in the teas sold in Warsaw various foreign leaves, which they identified by their anatomical characters.

leaves in tea, chemistry cannot be expected to play a very active part, though it sometimes affords very useful indications. Thus A. Wynter Blyth has pointed out (*Analyst*, ii. 39) that a crystalline sublimate (which he believes to be theine) is obtainable from a single leaf of tea. For this purpose he boils the leaf for a minute in a watch-glass with a very little water, adds an equal bulk of calcined magnesia, and evaporates the mixture rapidly to a large drop, which is transferred to a microscopic covering glass and evaporated nearly to dryness on a heated iron plate. It is then covered by a ring of glass, and when the moisture is nearly driven off a second slip of glass is added as a cover. At a somewhat higher temperature theine volatilises, and on examining the deposit on the covering under the microscope may be recognised by its characteristic appearance. Other leaves than tea may give a crystalline sublimate, but if no sublimate is obtained the leaf cannot be a product of the tea-plant.

A. W. Blyth has also proposed to utilise the constant presence of manganese in tea-leaves as a means of recognising them. If a single tea-leaf be ignited in platinum, and the ash taken up in a bead of sodium carbonate contained in a loop of platinum wire, on remelting the flux after a minute addition of nitre the green colour of the sodium manganate will be distinctly recognisable. Or a minute quantity of nitre and carbonate of sodium can be at once added to the ash on the platinum foil, when on fusing the mixture a distinct green colour will be obtained if manganese be present.

The author has found manganese in the leaves of *Camellia Thea* (tea), *Camellia Japonica*, *Camellia sasanqua*, *Coffea Arabica*, beech, blackberry, and sycamore. Manganese was absent from the leaves of the hawthorn, ash, raspberry, cherry, plum, and rose; and only faint traces were detected in the leaves of the *Ilex Paraguayensis*, elm, birch, lime, sloe, elder, willow-herb, and willow.

For the detection and identification of foreign leaves in tea, the botanical and microscopical characters are best fitted. Some of the sample to be examined should be put into hot water, and

Among the leaves recognised were those of *Epilobium angustifolium*, or French willow-herb, which formed the great part of the "tea" sold in certain localities. They also found the leaves of *Epilobium hirsutum* (great willow-herb), *Ulmus campestris* (elm), *Prunus spinosa* (sloe), *Fragaria vesca* (strawberry), *Fraxinus excelsior* (ash), *Sambucus nigra* (elder), *Rosa canina* (dog-rose), and *Ribes nigrum* (black currant). The infusion of willow-herb is darker than that of tea, and gives a precipitate of mucilage on treatment with alcohol.

An article known in Russia as "Karpar tea" also contains an admixture of the leaves of *Epilobium angustifolium*. Two samples examined by J. Nikitinsky in 1885 yielded 7·87 and 10·43 per cent. of ash, six representative genuine teas yielding from 5·60 to 6·87 per cent.

when the leaves have unfolded they are spread out on a glass plate and held up to the light, when, with the aid of a lens, the venation, serration, &c., can be readily observed. A valuable aid to the examination consists in treating the leaves with a solution of sodium hypobromite, or, as suggested by A. Wynter Blyth, a strongly alkaline solution of potassium permanganate. In using the reagent, the leaf should be enclosed between two microscopic cover-glasses, a weight being placed on the upper one to keep it in position. On heating the leaf with the reagent, action at once commences, the colouring matter being first attacked and subsequently the cell-membranes. When the action is sufficiently advanced, the leaf is removed, washed, and immersed in hydrochloric acid, which leaves the leaf as a translucent white membrane in which the details of structure can be readily observed. J. Bell removes the skin of the leaf by immersing it in "water containing a few drops of nitric acid," and gradually heating to the boiling-point, when the skin rises in blisters, and may be readily removed by a camel's-hair brush.

The primary venation of the tea-leaf consists of a series of well-defined loops, which are not met with in most leaves likely to be used as adulterants. The serrations are not mere saw-teeth on the margin of the leaf, but actual hooks.[1] The serration stops short abruptly at some distance from the base. The Assam tea-leaf is sometimes biserrate. At the apex of the tea-leaf there is a distinct notch, instead of a point. The epidermis of the under-surface is seen under the microscope to consist of distinct sinuous cells, with numerous oval stomata, and a few, long unicellular hairs.[2] On the upper surface the stomata are less numerous. If the under surface of the tea-leaf be examined under the microscope after separation of the cuticle, the peculiar and characteristic space between the twin cells of the stomata may be readily perceived.

T. Taylor has pointed out the presence of "stone cells" in the leaves of tea and *Camellia Japonica*, and confirms the observations of Blyth as to the absence of these formations in the leaves of the willow, sloe, beech, ash, black-currant, raspberry, and *Ilex Paraguayensis*. Taylor prepares the leaves for examination by boiling them in a strong solution of caustic potash or soda.

[1] The serrations are very strongly marked on mature leaves, but are indistinct or almost wanting in the delicate leaf-buds which constitute "flowery pekoe."

[2] Tea-hairs are conical, pointed, slightly bent towards the base. They have very thick walls, and the central duct usually contains granular matter. Numerous hairs are observable on young tea-leaves, but on old leaves they are sometimes wholly wanting.

In the leaf of the blackthorn or sloe (*Prunus communis* or *P. spinosa*)[1] the serratures are direct incisions, numerous, often irregular, and extending to the base. There are no spines. The cells of the epidermis are not sinuous, and are much smaller than those of tea, especially on the under surface. The cells on the upper surface are striated. The stomata of the sloe-leaf are smaller and less numerous than those of tea. The hairs are shorter and coarser than those of the tea-leaf; are marked in a peculiar manner, and have a club-shaped enlargement at the base.

The leaf of the elder (*Sambucus nigra*) is more pointed than that of the tea-plant, and the lobes are unequal at the base. The serrations are direct incisions. The midriff has hairs on it, and on the leaf itself there are two distinct kinds of hairs—one, a short, spinous hair, and the other jointed and club-like.

In the leaf of the willow (*Salix alba*) the serrations much resemble those of tea, but the cells of both the upper and under epidermis are much smaller than in tea, and the walls are not sinuous. The hairs, which are very abundant on both sides of the leaf, are long, unicellular, and sinuous. The elongated form of the willow-leaf and the character of the venation also distinguish it from tea.

The appearance of the leaf of the hawthorn (*Cratægus monogyna* and *C. oxyacantha*) is well known. The cells of the epidermis are mostly quadrilateral, with very sinuous outlines, especially on the under surface. The stomata are oval or nearly round, large, and numerous.

The leaves of the beech (*Fagus sylvatica*) are ovate, obscurely dentate, with parallel venations running right to the edge.

The leaves of *Chloranthus inconspicuus* are long, oval, serrated, wrinkled, with venations running nearly to the edge, and there by their intersection forming little knots which give the margin of the leaf a very rough feeling. The cells of the epidermis are very large, and the stomata oval and rather numerous.

The leaves of *Camellia sasanqua* are oval, only obscurely serrate if at all, and of a tough leathery texture. The lateral veins are inconspicuous. Both the upper and lower epidermis show a peculiar dotted or reticulated structure, and the lower is studded with numerous small oblong stomata.

The leaves of *Lithospermum officinale* (the common gromwell) have been extensively used in Bohemia for adulterating tea. They

[1] A specimen of sloe-leaves gathered early in September gave, after drying, the following results (in the author's laboratory):—Moisture, 6·40 per cent.; insoluble matter (on whole leaves), 55·90; tannin (by gelatin), 16·00; gum, &c., 8·90; total ash, 8·74; and ash soluble in water, 4·70 per cent.

greater part from India. Brazil at the present time furnishes about one-half of the world's supply of coffee.[1]

Commaille (*Monit. Scient.*, [3], vi. 779) gives the following as the chemical composition of undressed Mysore coffee :—Moisture (from 24 samples), 6·3 to 15·7 per cent. ; fatty matters, 12·68 ; glucose, 2·60 ; legumin-casein, 1·52 ; albumin, 1·04 ; caffeine, 0·42 to 1·31 ; and ash, 3·88 per cent.

O. Levesie (*Arch. Pharm.*, [5], iv. 294 ; *Jour. Chem. Soc.*, xxxi. 752) obtained the following range of figures by the analysis of seven typical samples of raw coffee :—

Caffeine,	0·64	to	1·53	per cent.
Gummy matter,	20·6	,,	27·4	,,
Fat,	14·76	,,	21·79	,,
Tannic and caffetannic acids,	19·5	,,	23·1	,,
Cellulose,	29·9	,,	36·4	,,
Ash,	3·8	,,	4·9	,,

J. Bell (*Analysis and Adulteration of Foods*, i. 43) gives the following analyses of typical samples of raw and roasted coffee :—

Bengal plant has smaller leaves than the Jamaica coffee, and very small berries. The Liberian coffee-plant (*Coffea Liberica*) appears to be a distinct species, which is little subject to disease, and has been successfully introduced into the East Indies.

The coffee fruit usually, but not always (see above), contains two twin seeds, which touch each other on the flattened surface. These are contained in a pulp which is removed by water and a process of fermentation ; and the membranous pericarp (technically termed "parchment") which incloses each seed is removed by rollers and winnowing.

The *parchment* from coffee-berries is imported to England in considerable quantities, and, when roasted, is said to form an ingredient of the beverage sold in cheap coffee-shops.

An analysis of unroasted "parchment," made in the author's laboratory by C. M. Caines, showed it to contain :—Water, 9·43 ; essential oil, 0·068 ; caffeine, 0·27 ; hot-water extract, 1·61 ; total ash, 10·41 ; and soluble ash, 0·19 per cent. A somewhat coffee-like aroma was developed by roasting.

It is stated that the Arabs in the neighbourhood of Jedda discard the kernel of the coffee-berries and make an infusion of the husks (*Pharm. Jour.*, [3], xvii. 656).

[1] In Australia, an infusion of slightly roasted coffee-leaves is drunk in the same manner as tea. Its taste suggests at once that of tea and tobacco. The leaves, when burnt or roasted, exhale a powerful odour of tobacco, and the smell of the condensed vapours strongly suggests that of tobacco-juice. O. Hehner, who has analysed the leaves (*Analyst*, iv. 84), found only 0·29 per cent. of caffeine.

	Mocha Coffee.		East Indian Coffee.	
	Raw.	Roasted.	Raw.	Roasted.
Moisture, ...	8·98	0·63	9·64	1·13
Caffeine, ...	1·08	·82	1·11	1·05
Saccharine matter, . . .	9·55	·43	8·90	·41
Caffeic acids, ...	8·46	4·74	9·58	4·52
Alcoholic extract, containing nitrogenous and colouring matter, ...	6·90	14·14	4·31	12·67
Fat and oil, ...	12·60	13·59	11·81	13·41
Legumin and albumin, . . .	9·87	11·23	11·23	13·13
Dextrin, ...	·87	1·24	·84	1·38
Cellulose and insoluble colouring matter, ...	37·95	48·62	38·60	47·42
Ash, ...	3·74	4·56	3·98	4·88
	100·00	100·00	100·00	100·00

Bell believes the sugar of coffee to be a peculiar species, possibly allied to melezitose. G. L. Spencer, on the other hand, has definitely proved that the carbohydrates of coffee consist very largely of sucrose, which he has isolated in considerable quantities. There is likewise present a body which yields galactose on hydrolysis, as also a pentose-yielding gum.

Caffetannic Acid, $C_{15}H_{18}O_8$, called by Payen chlorogenic acid, exists in coffee-berries in the proportion of 3 to 5 per cent., probably as a calcium or magnesium salt, or, according to Payen, as a double caffetannate of potassium and caffeine. It is prepared by diluting an alcoholic infusion of coffee with water, filtering from precipitated fatty matter, and precipitating the boiling filtrate with lead acetate.[1] On decomposing the washed precipitate with sulphuretted hydrogen free caffetannic acid is obtained. It forms a yellowish-white powder, or groups of colourless mammillated

[1] W. H. Krug determines caffetannic acid as a lead salt. He treats 2 grammes of coffee with 10 c.c. of water, and digests for 36 hours, then adds 25 c.c. of rectified spirit, and digests 24 hours more. The liquid is filtered, the residue washed with rectified spirit, and the filtrate heated to the boiling-point. A boiling concentrated solution of lead acetate is added, which throws down a precipitate of $Pb_3(C_{15}H_{15}O_8)_2$. When this has become flocculent it is filtered off, washed with alcohol till the washings are free from lead, washed with ether to remove traces of fat, dried at 100°, and weighed.

crystals. It is very soluble in water, less soluble in alcohol, and only very sparingly in ether. Caffetannic acid has an astringent taste, and the solution strongly reddens litmus. It gives a dark green coloration with ferric chloride, and precipitates the sulphates of quinine and cinchonine; but not gelatin, ferrous salts or tartar-emetic. It reduces silver nitrate on heating, forming a metallic mirror. The salts turn green in the air.

On dissolving caffetannic acid in caustic alkali or ammonia, and exposing the solution to the air, the liquid acquires a bluish-green colour owing to the formation of the oxidation-product, viridic acid, which is an amorphous brown substance, very soluble in water to form a solution which is turned green by alkalies. It gives a bluish-green precipitate with baryta-water, and a blue with lead acetate. Viridic acid dissolves in concentrated sulphuric acid to form a crimson solution, which on dilution with water gives a flocculent blue precipitate.

On prolonged boiling with caustic alkalies, caffetannic acid is split up into a sugar and caffeic acid, $C_8H_8O_4$, which crystallises from the neutralised liquid and has the constitution of a dihydroxy-cinnamic acid. By fusion with caustic potash, caffetannic acid yields protocatechuic and acetic acids. Heated alone it gives catechol.

ROASTING OF COFFEE. During the process of roasting, the aroma of coffee is developed and the toughness of the beans destroyed, so that subsequent grinding is facilitated. If the roasting be insufficient, the rawness is not destroyed and the flavour not fully developed; while if over-roasted, the product has a nauseous empyreumatic flavour.

When roasted to a yellowish-brown, coffee loses, according to Cadet, about 12½ per cent. of its weight, and in this state is difficult to grind. When roasted to a chestnut-brown it loses 18 per cent., and when it becomes entirely black, though not all carbonised, it has lost 23 per cent. In practice, the loss of weight in roasting coffee is between 12 and 20 per cent. (of which about 8 per cent. represents water removable at 100° C.), and if the latter figure is reached, the product is injured. According to Watson Will, the usual yield of roasted coffee is about 98 lbs. from 1 cwt. of raw berries. This corresponds to a loss of 12·5 per cent.

König found that on roasting coffee-berries to a light brown the total loss of weight was 17·77 per cent., of which 8·66 was water and 9·11 per cent. organic matter. The original coffee contained 11·19 per cent. of moisture, and after roasting, still retained 3·19 per cent. Eliminating this extraneous water from the results,

the percentage composition of the raw and roasted coffee was as follows :—

	Raw.	*Roasted.*
Caffeine,	1·33 per cent.	1·42 per cent.
Fat,	14·01 ,,	16·14 ,,
Albuminous matters,	11·43 ,,	12·31 ,,
Sugar,	3·66 ,,	1·35 ,,
Undefined non-nitrogenous matters,	34·55 ,,	39·84 ,,
Cellulose,	31·24 ,,	25·07 ,,
Ash,	3·92 ,,	3·87 ,,
	101·04 (!) per cent.	100·00 per cent.
Total matters soluble in water,	30·93 per cent	28·36 per cent.

According to Paul and Cownley (*Pharm. Jour.*, [3], xvii. 655, 821) there is no appreciable loss by volatilisation of caffeine during the roasting of coffee, unless the process is carried to excess. But Paul admits that the water condensed in the place leading from the roasting often contains some caffeine, which he considers has been probably carried over mechanically (*Pharm. Jour.*, [3], xvii. 821). Watson Will (*ibid.*, page 684) states that he has never failed to find caffeine in the sublimate obtained in coffee-roasting.

The chemistry of the roasting of coffee has been studied by O. Bernheimer (*Monatsch. Chem.*, i. 456 ; *Jour. Chem. Soc.*, xlii. 230), who roasted coffee till it had lost about 25 per cent. of its weight.[2] The uncondensible vapours consisted chiefly of carbon

[1] Paul points out that the caffeine exists in coffee in the form of caffetannate, which compound will not suffer decomposition at the ordinary temperature of roasting. Considering the great facility with which salts of caffeine undergo decomposition, this statement seems to require confirmation.

[2] Fifty kilogrammes of coffee yielded 5 litres of aqueous distillate and 680 grammes of solid matter floating thereon. On agitating this with ether, fatty acids, quinol and caffeol were extracted, while caffeine, acetic acid, methylamine and trimethylamine remained in the aqueous liquid. On evaporating the ethereal solution, and fractionally distilling the residual dark, coffee-smelling oil, a few drops of an acetone-like liquid passed over, followed by a little acetic acid and water. Between 200° and 300° caffeol distilled, and above that temperature palmitic and other solid fatty acids. On neutralising these and the 200°-300° fraction with sodium carbonate, a viscid dark oil was thrown down,

dioxide, and by passing them through dilute hydrochloric acid a resinous substance having the appearance of pyrrol-red was deposited. Among the solid and liquid bodies volatilised, Bernheimer found:—Palmitic and other solid fatty acids, 0·48 per cent.; caffeine, 0·28 per cent.; caffeol, 0·05 per cent.; besides water and acetic acid. Quinol, pyrrol, acetone, methylamine, and trimethylamine also occurred as secondary products.

CAFFEOL, $C_8H_{10}O_2$, is an oily liquid smelling very strongly of coffee, and no doubt is the substance to which the aroma of roasted coffee is due. It may be obtained by distilling roasted and powdered coffee with water, shaking the distillate with ether, and evaporating.

Caffeol boils at 196°, and is not solidified by a freezing mixture. It is not sensibly soluble in cold water, to which, however, it imparts its characteristic odour. It is slightly soluble in hot water, very slightly in aqueous potash, and with great facility in alcohol and ether. The alcoholic solution gives with ferric chloride a red coloration, not destroyed on adding ferric chloride. By fusion with caustic potash, caffeol yields salicylic acid, and, according to Bötsch (*Monatsch. Chem.*, ii. 621; *Jour. Chem. Soc.*, xlii. 174), is isomeric with methyl-salicyl alcohol, the two compounds having the following constitution:—

$C_6H_4(O.CH_3).CH_2OH$	$C_6H_4(OH).CH_2.OCH_3$
Methyl-salicyl alcohol.	Caffeol.

Paul and Cownley (*Pharm. Jour.*, [3], xvii. 822) found that on infusing coffee in six times its weight of boiling water, about 88 per cent. of the caffeine passed into solution. Three fluid ounces of such an infusion contained 2·36 grains of caffeine. As the medicinal dose of caffeine is from 1 to 5 grammes, a cup of coffee may be expected to have a marked effect as a stimulant.

The dietetic value of coffee is possibly dependent as much upon the presence of caffeol as on that of caffeine. According to M. Fargas, the effect of caffeol on the heart's action is the opposite to that of caffeine, and increases the strength and rapidity of the pulsations.

According to Couty, Guimaraes, and Niobey (*Compt. Rend.*, xcix. 85) coffee diminishes the activity of the simple combustions which produce carbon dioxide, but increases the forma-

which was separated from the aqueous solution of soap and washed with water containing a little caustic alkali. This dissolved out quinol, which was isolated by acidulating the washings and extracting with ether. The viscid oil, consisting of impure caffeol, was dried by calcium chloride and fractionally distilled, when the greater part passed over between 195° and 197°.

tion and excretion of urea, and the assimilation of meat and other nitrogenous foods. It is a complex aliment which renders the organism capable of consuming and destroying larger quantities of nitrogenous substances, and hence may be regarded as an indirect source of available energy.

Commercial coffee is subject to a variety of sophistications, both in the form of berry and after grinding. So far as the United Kingdom is concerned, the majority of the frauds formerly practised are obsolete, or nearly so, but certain illicit practices subsist.

COFFEE-BERRIES vary considerably in *size* and character according to their origin.[1] The following table shows the number of seeds required to fill a 50 c.c. measure (Thorpe's *Dict. Applied Chem.*, ii. 578):—

Fine brown Java,	187	Good ordinary Java,	223
Fine Mysore,	198	Fine Ceylon plantation,	225
Fine Neilgherry,	203	Good average Rio,	236
Costa Rica,	203	Medium Ceylon plantation.	238
Good ordinary Guatemala,	207	Manilla,	248
Good La Guayro,	210	Ordinary Mocha,	270
Good average Santas,	213	West African,	313
Fine long-berry Mocha,	217		

According to L. Padé (*Bull. Soc. Chim.*, xlvii. 501), raw coffee which has been damaged by sea-water is sometimes washed, decolorised with lime-water, again washed, dried rapidly, and coloured either by slight roasting or by dyeing with azo-oranges. By such manipulations, green Santas coffees are said to be increased 25 per cent. in value, and made to pass for Java growths. E. Waller states that South American coffees are often exposed to a high moist heat, which changes their colour from green to brown, in imitation of Java coffee. He found coffee-berries coloured with Scheele's green, yellow ochre, chrome-yellow, burnt umber,

[1] West Indian coffee-berries are regular in size, pale yellowish, firm and heavy, with a fine aroma, and they lose comparatively little on roasting. Brazilian coffee is larger, less solid, greenish or white, and usually classed as "low" or "low middling." Javanese coffee-berries are smaller, slightly elongated, light, and deficient in aroma and essential oil. When new, Java coffee is pale yellow, and of less value than when old and brown. The deeper colour is due to curing as well as age. It has been artificially coloured. Ceylon produces all descriptions of coffee, but the ordinary plantation coffees are even-coloured, slightly canoe-shaped, strong in aroma and flavour, heavy, and more susceptible of adulteration than the other kinds. Genuine Mocha coffee is small and dark yellow in colour, and considered of the highest quality.

venetian red, &c. When possible, such facings should be detached by agitating the berries with cold water and examining the sediment. Organic colouring matters can be detected by soaking the berries in alcohol, which is not coloured by genuine coffee. On evaporating the alcoholic solution to dryness, and taking up the residue in water, a solution will be obtained which will give the characteristic reactions of the coal-tar dyes.

The *specific gravity* of twenty-four samples of genuine raw coffee-berries was found by Padé to range from 1·368 to 1·041, while the density of the same samples, after roasting in the ordinary manner, varied from 0·635 to 0·500. Raw coffee which is lighter than water may be suspected of having been damaged by sea-water or other means, and subsequently washed and improved in colour by partial roasting.

The specific gravity of coffee-berries is ascertained by Padé by a special apparatus described in his paper. In the case of unroasted coffee, the gravity can be readily observed by immersing a few of the berries in saturated brine, which is then diluted with water till the coffee remains suspended in the liquid, the specific gravity of which is then taken. With roasted coffee, the brine must be replaced by the very lightest gasolene, the density of which can be increased if necessary by the gradual addition of ordinary kerosene. Another plan of ascertaining the specific gravity of coffee-berries is to introduce as many as possible into a tared 50 c.c. flask or other vessel of known capacity. The weight is then ascertained, and the flask filled to the mark with mercury. The weight is again observed, when the increase will be the weight of mercury required to fill the interstices between the berries:—

$$\frac{\text{Weight of berries in grammes} \times 13{\cdot}59}{(\text{Measure of vessel in c.c.} \times 13{\cdot}59) - \text{weight of interstitial mercury}} = \text{sp. gr. of berries.}$$

According to J. König (*Zeitsch. angew. Chem.*, 1888, page 680) coffee is often roasted with an addition of glucose-syrup, which makes the decoction look stronger, and causes the berries to hold an additional 7 per cent. of water.[1] L. Padé states that roasted

[1] Coffee so treated yields from 6 to 8 per cent. of soluble matter on agitation with cold water, while coffee roasted without sugar yields from 4 to 5 per cent. only. In the former case, Fehling's solution indicates from 1 to 1½ per cent. of reducing sugar, against 0·2 to 0·5 in genuine coffee. Stutzer and Reitnair detect glucose by violently agitating 20 grammes of the coffee-beans with 500 c.c. of water for five minutes. The liquid is further diluted to 1000 c.c. and 50 c.c. of the filtered liquid evaporated to dryness at 100°. The dry residue is weighed, ignited, and the ash deducted. Pure roasted

coffee-beans can be made to take up nearly 20 per cent. of water by steaming them and coating them with glycerin, palm-oil, or vaseline to prevent evaporation. The specific gravity of the berries is thereby raised to 0·650–0·770, and hence is sensibly above 0·635, which is the maximum figure for genuine roasted berries.

Van Hamel Roos (*Revue Intern. des Falsifications*, May 15, 1891) has called attention to an ingenious method of sophisticating coffee-berries. A sample examined by him had the microscopic structure of genuine coffee, but showed an almost entire absence of fat globules, and gave an ether-extract of less than 1 per cent. (instead of 12 to 14). Roos suggests that the berries had been used for preparing coffee-extract, and then re-roasted with addition of a little sugar.

As a coating for coffee, T. W. Moore has patented (*Eng. Pat.*, 5033, 1889) a mixture of milk or condensed milk, ground or powdered glue, "liquid glycerin," and refined lard; with the addition in some cases of bicarbonate of soda, fine salt, and vinegar!

Imitation coffee-berries were formerly manufactured of fire-clay. These were mixed with genuine berries and roasted with them, when they absorbed some of the colouring matter and oil, and so remained a close imitation. On breaking such spurious berries the colour would be seen to be principally on the exterior. The determination of the total ash and silica would at once lead to the detection of such a fraud.

In 1850, Messrs Duckworth of Liverpool took out a patent for moulding chicory into the form of coffee-berries, and quite recently several kinds of factitious coffee-beans have been described.

A factory for the manufacture of imitation coffee-berries on the scale of 40 to 50 kilogrammes daily was recently seized at Lille by the French Government. It appeared in evidence that the composition of the product was:—Chicory, 15 kilogrammes; flour, 35 kilogrammes; ferrous sulphate, ½ kilogramme.

Factitious coffee-beans recently seized in Roumania consisted of coffee-grounds, chicory, and peas.

In America there are several firms which extensively manufacture imitation coffee-beans and "coffee-pellets." These preparations usually consist of wheat-flour, chicory, bran, and occasionally coffee. Samples purchased and examined by the chemists of the U.S. Department of Agriculture gave the following results:—

coffee shows from 0·44 to 0·72 per cent. of soluble organic matter, and gives a solution only faintly coloured; but if roasted with sugar or glucose the organic extract ranges from 1·81 to 8·18 per cent., and the liquid is more or less strongly coloured.

Appearance.	Specific Gravity.	Composition.
Roasted beans, . .	1·195	Wheat-flour.
Roasted beans, . .	1·198	Wheat-flour, coffee, and chicory.
Roasted beans, . .	1·111	"Kunst Kaffee." Wheat-flour, coffee, and chicory.
Roasted pellets, . .	1·119	Wheat-flour, bran, and probably rye.
Roasted pellets, . .	1·183	
Roasted pellets, . .	1·193	
Raw beans, ...	...	Wheat-flour and coffee.
Roasted beans, . .	1·211	Wheat-flour.
Light-coloured beans,	1·174	Wheat-flour and probably sawdust.
Dark-coloured beans,	1·134	
Roasted beans, . .	1·118	Wheat-flour.
Roasted granules, .	...	Hulls of peas, with molasses.
Roasted lumps, . .	...	Bran and molasses.
Roasted granules, .	...	Pea hulls and bran.

A. W. Rehnstrom (*Eng. Pat.*, 14,970, 1889) has described a substitute for coffee prepared by boiling down whey or milk in a vacuum to a pasty consistency, forming the product into cakes, drying it below 100°, cutting it into pieces the size of coffee-beans, and roasting.

L. Jaunnes, in 1891, examined a factitious coffee consisting of acorns and cereals.

An imitation coffee examined by J. König (*Zeitsch. angew. Chem.*, 1888, page 680) closely resembled real coffee in appearance, but all the berries were precisely the same shape. Under the microscope, wheat-starch was detected, and König concluded that the article consisted of roasted wheat dough of low quality. E. Fricke (*Zeitsch. angew. Chem.*, 1889, page 310) has described a factitious coffee containing caffeine, and apparently made from lupine-seeds (compare page 544). K. Portèle (*Chem. Centralbl.*, 1890, page 135) has described factitious coffee-beans sold under the name of "Kunst Kaffee." The following were the compositions of the samples referred to above:—

	Portèle.	*König.*	*Fricke.*
Moisture, ...	1·46 per cent.	5·14 per cent.	(Analysed after drying.)
Proteids, ...	13·93 „	10·75 „	17·90 per cent.
Fat, ...	3·86 „	2·19 „	2·03 „
Starch, sugar, gum, &c., .	64·01 „	76·76 „	...
Cellulose, ...	15·83 „	3·96 „	10·83 „
Caffeine, ...	0·07 „	...	0·94 „
Ash, ...	2·53 „	1·20 „	2·27 „
	101·63 per cent.	100·00 per cent.	100·00 per cent.
Matter soluble in water, .	21·53 per cent.	29·28 per cent.	24·85 per cent.

R. Wolffenstein (*Zeitsch. angew. Chemie*, 1890, No. 3) has described two varieties of factitious coffee, respectively known in

Germany as *Domkaffee* and *Allerweltkaffee*. Both preparations were entirely destitute of caffeine. One consisted practically of chicory, while the other contained large quantities of lupines. From the latter specimen Wolffenstein isolated a brown colouring matter having the spectroscopic and chemical characters of *Cassella-brown*. It was soluble in alkalies and in water, but was completely precipitated from its solutions by hydrochloric acid. Fourteen grammes of the sample extracted with water and precipitated with acid yielded 1·67 gramme of the colouring matter (!).

Factitious coffee-beans are, with very rare exceptions, heavier than water, while genuine roasted beans are invariably lighter, unless much over-roasted. In taking the specific gravity, twenty beans should be immersed in brine, which is then diluted with water till ten of the beans float and the remainder sink. The result shows the average density; but individual factitious beans often vary considerably from the mean.

In genuine coffee-beans a portion of the fine membrane or "parchment" with which the berries were invested will almost always be found adhering in the cleft. The microscopic structure of the bean, as seen in a thin section, or of the powder affords a certain means of recognising its nature. Most factitious beans contain starch, which is entirely absent from genuine coffee. Chicory and other roots are readily recognisable by the microscope. The methods used for the examination of ground coffee may also be applied.

Dangway beans, the seeds of *Cassia tora* or *C. occidentalis*, abundant in British Burmah, have been prepared and patented as a substitute for coffee (*Eng. Pat.*, 15,564, 1888). In Germany, the ground and roasted seeds have been sold under the name of "Mogdad coffee," and it is said that a smaller proportion than 20 per cent. in coffee cannot be detected either by the taste or the appearance of the sample. Dangway beans leave about 10 per cent. of ash on ignition, and have a characteristic microscopic appearance which has been described and illustrated by A. Wynter Blyth (*Food; Composition and Analysis*). They sink very rapidly in water and colour brine more intensely than do coffee beans. Dangway beans contain a tannin distinct from caffetannic acid. They are destitute of caffeine, but O. Hehner has detected a minute quantity of some other alkaloid.

The use of *Mussaenda Borbonica* seeds, to be mixed and roasted with coffee-beans or entirely substituted for them, has also been patented (*Eng. Pat.*, 14,945, 1888).[1]

[1] Investigations at Kew Gardens show the supposed *Mussænda* seeds to be really those of *Gærtnera vaginata*. They contain no caffeine.

The beans of a species of *Phaseolus* are reported by E. Fricke to be roasted, ground, and sold as "Congo coffee." The berries are very large—214 filling a 100 c.c. measure—and of shining black colour. The infusion is very astringent and contains no caffeine or other crystallisable alkaloid.

To distinguish lupine-seeds from coffee-beans, Hager treats 3 grammes of the powdered sample with 20 c.c. of water and filters after half an hour. The filtrate from genuine coffee will be feebly yellow and not taste in the least degree bitter, while in the presence of lupine-seeds a marked bitter taste will be observed.

GROUND COFFEE. Besides the foregoing sophistications and substitutions of the coffee-bean, ground coffee is liable to various adulterations.[1] Some of these can be tolerated when practised in moderation, provided that the fact and proportion of admixture are duly acknowledged; but it must be remembered that all these additions, including *chicory*, the least objectionable and by far the most widely used,[2] are destitute of the volatile oil and peculiar alkaloid which give to coffee its most valued properties. The diminished consumption of coffee in England is doubtless largely due to the frequency and extent of its sophistications.

[1] The late Dr Wm. Wallace, writing in 1884 (*Analyst*, ix. 42), names the following articles as used for adulterating coffee:—Chicory, caramel, dried and roasted figs, dried dates, date-stones, decayed ship biscuits, beans, peas, acorns, malt, dandelion root, turnips, carrots, parsnips, and mangold-wurzel. Damaged raisins are stated by Albert Smith to be used together with chicory for making French coffee.

[2] COMMERCIAL CHICORY is prepared from the root of *Cichorium intybus*, which is cut into slices, kiln-dried, and then roasted in the same manner as coffee, usually with the addition of a small proportion of fat of some kind. The preparation and use of roasted chicory appears to have originated in Holland about 1750. A. Mayer (*Bied. Central.*, 1885, page 828) gives the following as the composition of three samples of Dutch chicory root:—Water, 72·00 to 77·3 per cent.; albuminoïds, 1·1; fat, 0·2; inulin and other non-nitrogenous matters insoluble in alcohol, 12·00 to 17·3; crude fibre, 1·40 to 1·8; sugar, &c., 5·60 to 6·0; bitter extract, 0·05 to 0·15; and ash, 1·40 to 1·9 per cent. Mayer found the bitter substances extracted by chloroform to be soluble in water and alcohol, insoluble in ether, and absorbed by bone-charcoal. They were decomposed by boiling with dilute sulphuric acid, but did not by such treatment yield any substance capable of reducing Fehling's solution.

A. Petermann (*Bied. Central.*, 1883, page 843) gives the following results of analyses of two samples of roasted chicory, one of which was coarsely and the other finely ground. The ash was somewhat higher than usual, but was perfectly white. The *fat* shown was probably not all natural to the

The chief adulterations likely to be met with in ground coffee are:—(1) Mineral matters; (2) roots, such as chicory, dandelion, turnip; (3) seeds and seed-products, such as beans, acorns, and cereals; and (4) saccharine matters, such as caramel and roasted dates and figs.

In *Bulletin* No. 29 of the Laboratory of the Inland Revenue Department, Canada, the chief analyst, T. Macfarlane, states that:—"There are, moreover, large quantities of a substance imported under the name of essence of coffee, for adulterating purposes, which is a species of burnt sugar, and, from its containing dextrin, is probably made from some of the bye-products of the glucose factories. It costs in New York and Philadelphia from 3 to 5 cents per lb. As it possesses no organic structure it is apt to be overlooked in the microscopical examination. It contains about 75 per cent. of matter soluble in water, which has great colouring power, and a little of it is capable of imparting a strong brown coffee colour to water."

Caramel, when added as such, may often be distinguished under a low microscopic power by the jet-black colour of the particles. These dissolve easily in water with intense brown colour, and the solution has a bitter taste.

A factitious caramel is now manufactured by adding to glucose about one-eighth of its weight of a brown coal-tar dye, *naphthol-brown*.

A useful preliminary test for ground coffee consists in gently strewing some of the powder on the surface of cold water. The oil contained in coffee prevents the particles from being readily wetted by the water, thus causing them to float. Chicory and the

chicory, as the proportion recorded is largely in excess of that found by other observers. The water also is much above the usual proportion in recently roasted chicory (5 to 7 per cent.), and the albumenoids below the usual range (8·75 to 11·50.—O. Hehner).

	Coarse Grains.	Fine Powder.	
Water (lost at 100°–105° C.),	16·28	16·96	Soluble in hot water =57·96.
Glucose,	26·12	23·76	
Dextrin; inulin,	9·63	9·31	
Albuminoïds,	3·23	3·66	
Colouring matter and bitter extractive,	16·40	17·59	
Ash in soluble portion,	2·58	2·55	
Ash in insoluble portion,	4·58	5·89	Insoluble in hot water =26·14.
Albuminoïds,	3·15	2·98	
Fat,	5·71	3·92	
Cellulose,	12·32	13·37	

majority of coffee adulterants contain no oil, and their caramel is very quickly extracted by the water, with production of a brown colour, while the particles themselves rapidly sink to the bottom of the water.[1] On stirring the liquid, coffee becomes tolerably uniformly diffused without sensibly colouring the water, while chicory and other sweet roots quickly give a dark brown, turbid infusion. Roasted cereals do not give so distinct a colour.

According to A. Franz (*Arch. Pharm.*, [5], iv. 298), if 2 c.c. of a 10 per cent. infusion of coffee in boiling water be treated with 0·3 c.c. of a 2½ per cent. solution of cupric acetate, and the liquid filtered, a greenish-yellow filtrate is obtained. If chicory be similarly treated, a dark red-brown filtrate results, the colour of which changes on standing. Ten per cent. of the adulterant can thus be detected.

The colour of an infusion of chicory is said to remain unaltered on addition of a solution of ferric chloride or sulphate, while the brown colouring matter of coffee infusion turns green, and is partially precipitated as bluish-green flakes. In an infusion of mixed chicory and coffee, the reagent forms a precipitate, and leaves the liquid more or less brownish-yellow. The deposition of the precipitate is facilitated by rendering the liquid slightly alkaline by ammonia (*Dingler's polyt. Jour.*, ccxi. 78).

Albert Smith (*Pharm. Jour.*, [3], xi. 568) recommends, for the detection of chicory in coffee, that 10 grammes of the sample should be boiled with 250 c.c. of water, and the liquid strained and precipitated with a slight excess of basic lead acetate. On allowing the precipitate to settle, the supernatant liquid will be colourless if pure coffee has been under treatment, but in presence of chicory will be coloured to a greater or less degree according to the proportion present, which can be estimated from the depth of tint by a process similar to that of nesslerising water.

The three foregoing tests are occasionally of service for the examination of infusion of coffee when the solid article is not available, but they cannot be regarded as so satisfactory as the actual recognition of the adulterant by the microscope.

The great majority of seeds likely to be met with in coffee contain a notable quantity of *starch*. This is true of beans, peas, acorns, and all cereals and products therefrom. Hence if starch be absent, the freedom of the coffee from all this class of adulterants is certain. If present, the nature of the admixture can usually

[1] If a funnel be used for the above test, the sunken particles may be readily let out and examined under the microscope.

be ascertained by a microscopic examination of the prepared sample.[1]

For the detection of starch, the author boils the coffee for a few minutes with about 10 parts of water. When the liquid has become perfectly cold, some dilute sulphuric acid is added, and then a strong solution of permanganate of potassium dropped in cautiously, with agitation, till the colouring matter is nearly destroyed, when the liquid is strained or decanted from the dissoluble matter. On now adding a solution of iodine to the solution, a blue coloration will be produced if any starch be present. As little as 1 per cent. can be readily detected in this manner.[2]

Some operators employ animal charcoal for decolorising the coffee infusion before testing for starch. The addition of starch-holding adulterants to coffee, in the author's experience, is rare, but in the United States and Canada is very common, the adulterants there found including wheat-flour and bran, buckwheat, barley, maize, peas, pea-hulls, &c.[3]

The insoluble matter remaining after treating the coffee with water and decolorising with permanganate can be advantageously examined under the microscope for chicory and other non-starchy additions, the structure of which is more readily observed after the removal of the colouring matter.

F. M. Rimmington (*Pharm. Jour.*, [3], xi. 529) recommends, for the removal of colouring matter, that the sample of coffee should be boiled for a short time with water containing a little carbonate of sodium. After subsidence, the liquid is poured off, the residue washed with water, and then treated with a weak solution of bleaching powder until decolorisation is effected, which usually occurs in two or three hours. The real coffee will then form a dark stratum at the bottom of the beaker, and the chicory a light and almost white stratum floating above it, and showing a clear and sharp line of separation.

[1] For this purpose the coffee should first be exhausted with ether to remove fat, and then treated with methylated spirit to dissolve the colouring matter. In the residue, the starch and other structures will be readily perceptible.

[2] A certain famous sample of coffee alleged to contain acorns gave the author no reaction by the above test, but after the addition of 2 per cent. of roasted acorns the test showed the presence of starch very clearly.

[3] In 1875 a large seizure was made in the east of London of a mixture of 10 per cent. of coffee with 90 of roasted acorns. Roasted acorns were first placed before the English public as "Pelotas coffee," and subsequently as "coffee surrogate," but the manufacture of both these preparations was stopped by the excise.

Under the microscope, chicory is readily recognised by the peculiar dotted appearance of the vessels, often occurring in bundles, and by the characteristic appearance of the large cells. Dandelion, turnips, and other sweet roots present a close similarity to chicory, and can only be safely distinguished therefrom by careful microscopic comparison of the sample with the actual roots in question.

The microscopic appearance affords the only certain means of identifying chicory and other roots in coffee, and the same statement applies to saccharine fruits, such as roasted figs, dates, raisins, &c.[1]

The nature of an adulterant of coffee having been ascertained by the aid of the microscope or other means, an attempt may be made to deduce the proportion present from the chemical composition of the sample. When only one adulterant is present, this may sometimes be effected with a fair approximation to accuracy; but even in the case of chicory it is not always possible to ascertain the proportion within a somewhat wide limit.[2]

For ascertaining the *proportions* of adulterants in coffee, the only chemical distinctions of any practical value are:—Certain constituents of the ash; the proportion of fat as extracted by ether or petroleum spirit; the proportion of aqueous extract,

[1] Printed descriptions of microscopic characters are of little value, and drawings are often misleading. The adulterants of coffee are best examined as transparent objects under a moderate power, and, except where starch is to be identified, by unpolarised light.

[2] What can be done in this manner, and the errors liable to occur in practice with deficient methods or imperfect manipulation, is apparent from the following figures obtained in 1882 by various analysts to whom exactly similar samples of mixed coffee and chicory of known composition were submitted (*Analyst*, vii. 76):—

Actual percentage of Chicory in sample, .	10 per cent.	30 per cent.	37½ per cent.
Percentage of Chicory reported.			
Somerset House (Referees),	Not more than 2½ per cent.	Not less than 35 per cent.	Not less than 48 per cent.
A, ...	7 per cent.	31 per cent.	38 per cent.
B, ...	7 ,,	32 ,,	34 ,,
C, ...	5 to 10 per cent.	25 ,,	50 ,,
D, ...	16 per cent.	35 ,,	47 ,,
E, ...	Genuine.	31 ,,	50 ,,
F, ...	Upwards of 10 per cent.	Upwards of 30 per cent.	Upwards of 40 per cent.

as deduced from its weight or the specific gravity of the solution; the colour of the infusion; and the proportion of caffeine in the sample. In all cases of importance two or more of these methods should be employed.

A. Smetham (*Analyst*, vii. 73) obtained the following range of figures by the analysis of seven samples of roasted coffee, representing typical commercial qualities:—

Moisture (lost at 100° C.),	1·59	to	3·89	per cent.
Oil (ether extract),	10·13	,,	12·13	,,
Crude fibre,[1]	70·84	,,	74·50	,,
,, ,, in sample dried at 100°,	73·71	,,	75·70	,,
Cellulose,	26·34	,,	34·40	,,
Nitrogen,	2·14	,,	2·38	,,
Total ash,	4·08	,,	4·63	,
Soluble ash,	3·14	,,	3·60	,,
Ratio of total ash to soluble,	100 : 72	,,	100 : 82	,,

The following analyses by C. Krauth (*Ber.*, xi. 277; *Jour. Chem. Soc.*, xxxiv. 449) give some comparative figures for coffee and its more probable adulterants. Except in the case of the last column, the results apply to the substances previously dried at 100°:—

	Ash.	Fat.	Sugar.		Soluble in Water.	Insol. in Water.	Moisture in Undried Substance.
			Pre-existent.	After Boiling with Acid.			
Coffee, roasted, five samples,	4·19 to 6·38	11·76 to 15·6	0·2	24·29	22·47 to 25·21	74·79 to 77·53	1·47 to 4·37
Chicory, roasted,	10·83	1·15	23·40	22·14	65·42	34·58	4·30
Chicory, unroasted,	5·35	43	23·84	Not decerned	78·71	21·28	0·89
Rye, roasted,	2·43	1·68	...	75·37	31·92	68·07	0·28
Wheat, roasted,	1·80	2·75	...	...	52·65	47·35	...
Coffee, with 10 per cent. rye,	4·31	14·16	·19	29·65	25·98	74·46	2·15
Coffee, with 10 per cent. wheat,	5·10	12·55	2·30	23·15	30·63	69·36	2·30

[1] The "crude fibre" was determined by boiling 2 grammes of the sample with three successive quantities of water, and washing the residue on a counterpoised filter till the washings were colourless, when it was dried at 100° C. and weighed.

The following analyses by König show the composition of certain adulterants of coffee :—

	Chicory.	Figs.	Acorns.	Rye.
Water,	12·16	18·98	12·85	15·22
Nitrogenous matters,	6·09	4·25	6·13	11·84
Fat,	2·05	2·83	4·61	3·46
Sugar,	15·87	34·19	8·05	3·92
Other non-nitrogenous matters,	46·71	29·15	62·0	55·37
Cellulose,	11·00	7·16	4·98	5·35
Ash,	6·12	3·44	2·12	4·81
Matters soluble in water,	63·05	73·81	...	45·11 (?)

The following table shows the published results of analyses of coffee substitutes said to be manufactured respectively from acorns, rye, and barley :[1]—

	"Acorn[1] Coffee."	"Rye Coffee Substitute."	"Barley Coffee."	"Barley Coffee."
Water,	12·85	2·22	3·45	6·41
Nitrogenous matters,	6·13	11·87	9·38	10·56
Fat,	4·01	3·91	3·25	1·04
Sugar,	8·01	...	70·13 (Sugar, Starch, Dextrin, Other non-nitrogenous matters)	68·38
Starch,	62·00 (Starch, Dextrin, Other non-nitrogenous matters)	8·34		
Dextrin,		49·51		
Other non-nitrogenous matters,		9·83		
Cellulose,	4·98	9·78	4·25	10·56
Ash,	2·02	4·54	3·36	3·04
Matters soluble in water,	...	61·33	31·20	34·37
Glucose formed by boiling with dilute sulphuric acid,	...	...	69·28	67·19

Moscheles and Stelzer have recently published complete analyses of several coffee substitutes (*Chem. Zeit.*, 1892, xvi. 281; *Analyst*, xvii. 154). One of these contained lupines (which they consider a very reprehensible addition), and another was destitute

[1] The "acorn coffee" was analysed by König, who found from 20 to 30 per cent. of starch, and 6 to 8 per cent. of a variety of tannic acid. The "rye coffee substitute" was prepared by Behr Bros. The analyses of "barley coffee" are by C. Kornauth.

of coffee, but contained 0·31 per cent. of caffeine, due to the presence of powdered kola-nut.

The ash of pure coffee is generally between 3½ and 4½ per cent., rarely, if ever, exceeding 5 per cent., and even when a considerable proportion of chicory is present it seldom rises beyond 6 per cent. Any notably higher proportion will indicate the presence of a *mineral adulterant.* The ash should be white, or nearly so, any marked red tint indicating an added compound of iron.

The composition of the ash of coffee presents some marked differences from that of chicory, as is apparent from the following results of analyses by H. Ludwig (*Arch. Pharm.*, [3], i. 482) and James Bell (*Foods*, ii. 46, 57).

	Coffee-beans. H. Ludwig.		Coffee-beans, Eight Samples. J. Bell.	Chicory Root, Eight Samples. J. Bell.	
	Gneiss Soil.	Limestone Soil.		Deducting SiO_2 and Sand.	Including SiO_2 and Sand.
K_2O . . .	14·13	44·03	53·20 to 55·80	27·85 to 46·27	24·88 to 33·88
Na_2O . . .	5·84	5·85	Not detected	3·17 ,, 16·90	2·04 ,, 15·10
CaO	8·64	4·89	4·10 to 6·16	7·65 ,, 10·81	5·00 ,, 9·60
M_gO . . .	8·14	8·01	8·20 ,, 8·87	5·33 ,, 8·08	3·42 ,, 7·22
Fe_2O_3 . . .	16·54	1·96	0·44 ,, 0·98	3·50 ,, 8·29	3·13 ,, 5·32
P_2O_5 . . .	18·65	10·54	10·15 ,, 11·60	9·59 ,, 12·61	6·65 ,, 11·27
SO_3	15·28	1·64	3·09 ,, 5·26	8·38 ,, 11·78	5·38 ,, 10·53
Cl	Trace	0·98	0·26 ,, 1·11	5·03 ,, 6·08	3·28 ,, 4·93
CO_2	8·34	21·24	14·92 ,, 18·13	2·04 ,, 4·60	1·78 ,, 3·19
SiO_2 . . .	1·65	0·37	0·00 ,, 0·45	...	2·61 ,, 12·75
Sand . . .	None	None	None	...	8·08 ,, 23·10

Ludwig found in each case a notable amount of soda, a result which disproves Bell's improbable statement that this base is absent from coffee-ash. Ludwig's figures also show an enormous variation in the proportions of K_2O, Fe_2O_3, SO_3, and CO_2, according to the nature of the soil on which the coffee-plant is grown.[1] If the Na_2O in chicory-ash be calculated into its equivalent of K O, and the figure thus found added to the actual KO, the percentage is not greatly different from the proportion of potash found

[1] The sample of coffee from a gneiss soil must be regarded as highly abnormal. In the wide experience of the author the ash from genuine coffee has never been observed to have a red colour, as would be the case with the ash of a specimen containing a considerable proportion of iron.

by Bell in coffee-ash. The proportion of oxide of iron is notably greater in chicory than in coffee. Hence chicory-ash always has a red tinge which is absent from the ash of genuine coffee. A notable difference is observable in the proportions of CO_2 and Cl, and a very wide distinction in the figures for sand and silica. In only one of the eight samples of coffee did the silica even approach 0·5 per cent., and in another portion of the same coffee, which was properly screened before roasting, the silica of the ash fell to *nil*.

In consequence of the large proportion of potassium carbonate in coffee-ash, the percentage of the total ash soluble in water is much greater than in the case of chicory-ash, and attempts have been made to utilise this fact for ascertaining the proportion of chicory present in mixtures of the two. Thus the author found from 60 to 85 per cent. of the total ash of coffee to be soluble in water, whereas on an average only 34 per cent. of the total ash of chicory was soluble in water. But this proportion is gravely affected by the proportion of actual sand which may be present. This varies in commercial chicory from a trace up to 4·5 per cent., which difference is quite sufficient to invalidate deductions based on the ratio of the total to the soluble ash. By comparing the soluble ash with the total ash *minus* sand and silica, somewhat more reliable results are obtained, but at best the method is only capable of affording a rough indication of the proportion of chicory present. It may, however, serve to point to the presence of a foreign ingredient, which can then be identified and determined by other means. The following ash-analyses, by James Bell, are interesting in this connection :—

	Lupins.	Acorns.	Maize.	Parsnips.	Dandelion Root.
K_2O	33·54	54·93	30·74	56·54	17·95
Na_2O	17·75	0·63	Not found	Not found	30·95
CaO	7·75	6·01	3·06	6·85	11·43
MgO	6·18	4·32	14·72	6·49	1·31
Fe_2O_3	...	0·54	0·84	0·53	1·27
P_2O_5	25·53	11·15	44·50	13·84	11·21
SO_3	6·80	4·79	4·13	4·07	2·37
Cl	2·11	2·51	0·50	2·09	3·84
CO_2	0·56	13·69	...	11·44	6·21
SiO_2, &c.	0·87	1·01	1·78	0·57	11·26
	101·09	99·58	100·27	102·42	97·80

The following centesimal figures by Way and Ogston refer to the ash of other roots :—

	Turnip.	Beet.	Carrot.
Fe_2O_3 . . .	0·14 to 0·66	0·52 to 3·74	0·59 to 1·66
Cl . . .	3 ,, 5	85 ,, 30	3 ,, 4·6
CO_2 . . .	9·5 ,, 15	15 ,, 21·6	15 ,, 19

The *fat* of coffee is tolerably constant in amount, and hence the proportion serves as a useful indication of the amount of certain admixtures. Thomas Macfarlane, Head Chemist of the Inland Revenue Department, Ottawa, informs the author that the petroleum-ether extract from previously dried coffee ranges from 10 to 12 per cent. Only one sample out of nearly fifty examined showed less than 10, and no sample gave as much as 13 per cent., although 12½ per cent. was reached in a few inches. Chicory yields about 1 per cent. when similarly treated, and three samples of roasted barley gave from 1·31 to 1·54 per cent.

The aqueous extract of coffee is remarkably constant in amount, and is very little affected by variations in the roasting. Instead of weighing the actual extract, Graham, Stenhouse and Campbell (*Jour. Chem. Soc.*, ix. 38) determined the specific gravity of the aqueous infusions of coffee and various roasted vegetable matters. Their method was to treat the roasted substance with ten times its weight of cold water, raise the liquid to the boiling-point, and observe the density of the filtered liquid after cooling to 60° F. (= 15·5° C.). The following is a classified arrangement of their results :—

Substance.	Specific Gravity of 10 per cent. Infusion.	Substance.	Specific Gravity of 10 per cent. Infusion.
COFFEE :—		ROOTS :—	
Mocha, . .	1008·0	Chicory, Yorkshire,	1019·1
Neilgherry, .	1008·4	,, English, .	1021·7
Plantation Ceylon,	1008·7	,, Foreign, .	1022·6
Java, . . .	1008·7	,, Guernsey,	1023·3
Jamaica, . .	1008·8	Average,	1021·05
Native Ceylon, .	1009·0	Parsnips, . .	1014·3
Costa Rica, . .	1009·0	Carrots, . .	1017·1
Costa Rica, . .	1009·05	Turnips, . .	1021·4
Average, . .	1008·7	Dandelion, . .	1021·9
		Red beet, . .	1022·1
LEGUMINOUS SEEDS:—		Mangold wurzel, .	1023·5
Lupins, .	1005·7		
Peas, . . .	1007·3	CEREAL PRODUCTS :—	
Beans, . . .	1008·4	Brown malt, .	1010·9
		Black malt, . .	1021·2
MISCELLANEOUS :—		Rye meal, . .	1021·6
Spent tan, . .	1002·1	Maize, . . .	1025·3
Acorns, . .	1007·3	Bread raspings, .	1026·3

These results show a marked distinction between coffee, leguminous seeds, and acorns on the one hand, and cereal products and chicory and other roots on the other. Unfortunately, with the exception of chicory and coffee, they apply merely to single specimens of each kind of substance.

Experiments made in the author's laboratory gave a mean density for coffee-infusions precisely identical with that obtained by Graham, Stenhouse and Campbell (1008·7). Operating as they prescribe, however, there is always a suspicion that the exhaustion is incomplete, especially in the case of genuine coffee which has not been very finely ground. Hence in a series of experiments made in the author's laboratory, the sample of coffee was well boiled with 10 parts of water, the solution filtered, and the residue washed with hot water till the filtrate measured 10 c.c. for every 1 gramme of the substance employed. Operating in this manner, the infusions from fourteen specimens of ordinary commercial roasted coffee (ground in the laboratory) were found to have a specific gravity ranging from 1006·8 to 1008·5, with an average of 1007·9[1] (*Analyst*, v. 1).

J. Skalweit has shown that the specific gravity of the aqueous infusion is not sensibly affected by the extent to which the coffee has been roasted.

By the exhaustion-process, the author obtained the following results from samples of commercial chicory (undried):—

	Specific Gravity of 10 per cent. Infusion.
Yorkshire Chicory, under-roasted,	1025·9
,, ,, (same sample), highly roasted,	1019·0
Chicory of unknown origin,	1021·1
,, ,, ,,	1020·0
,, ,, ,,	1023·4
Mean,	1021·9

It is evident that the density of chicory infusions varies much more than that of coffee, a fact which prevents the method from furnishing more than an approximate determination of the proportion of coffee and chicory in a mixture of the two. A sharper result may be obtained by previously drying the sample at 100°,

[1] This figure is somewhat lower than the average of Graham, Stenhouse, and Campbell's experiments, which tends to show that they effected practically perfect exhaustion. The difference is not improbably due to a slight loss by evaporation when the infusion is made by raising the liquid to the boiling-point, instead of boiling thoroughly and making the infusion up to a definite measure after cooling. O. Hehner has met with a genuine coffee giving an infusion-density of 1010·2.

and hence eliminating the somewhat serious error due to varying proportions of moisture. Adopting 1024 as the normal gravity of the infusion of dried chicory and 1009 as that of dried coffee, the percentage of real coffee in a mixture of the two will be found by the following equation, where *d* is the specific gravity of the 10 per cent. infusion and C the percentage of coffee in the sample:—

$$C = \frac{(1024 - d)100}{15}.$$

A. McGill (*Trans. Royal Soc. Canada*, 1887) finds that the density of the infusions of coffee and chicory is materially affected by the fineness of the powder, the time occupied in heating the decoction to boiling, and the time during which the boiling with water is continued. He recommends that a weight corresponding to 10 grammes of the moisture-free sample should be boiled with 100 c.c. of distilled water in a flask fitted with a reflux condenser. The heat is adjusted so that ebullition commences in ten to fifteen minutes, and the boiling is continued exactly one hour, when the flame is removed, and after fifteen minutes' rest the liquid is passed through a dry filter. The average density of a 10 per cent. decoction of pure coffee thus prepared was found to be 1009·86 at 62°, the mean number for chicory decoction (three samples) being 1028·21 at the same temperature, or a difference of 18·35.[1] From these results the following formula may be deduced:—

$$C = \frac{(1028{\cdot}21 - d \text{ at } 62^\circ \text{ F.})100}{18{\cdot}35}.$$

[1] Thos. Macfarlane, Chief Analyst in the Inland Revenue Laboratory, Ottawa, has communicated to the author the following results, obtained by the application of McGill's method for ascertaining the infusion-density and actual determination of the soluble extract. This last determination was made by thoroughly extracting the dried sample with petroleum ether, and then treating the redried substance with boiling water. Instead of evaporating the solution, the insoluble matter was redried and weighed, the loss showing the "water extract":—

	Water Extract.	Infusion Gravity at 62° F.
Sontas Coffee,	22·44	...
Mocha Coffee,	21·92	1009·78
Java Coffee,	20·42	1009·73
„ with 10 per cent. Chicory,	25·90	1011·58
„ „ 20 „ „	30·75	1013·44
„ „ 30 „ „	37·40	1015·28
„ „ 40 „ „	43·36	1017·08
„ „ 50 „ „	49·84	1018·66
„ „ 60 „ „	53·82	1020·48
„ „ 70 „ „	60·34	1022·70
„ „ 80 „ „	65·93	1024·15
„ „ 90 „ „	71·41	1026·42
Chicory,	77·73	1028·32

It is evident that the specific gravity of the aqueous infusion is really a function of the solid matter dissolved by the water, and a close approximation to the percentage of the latter can be obtained by dividing the difference between the solution-density and 1000 by the number 0·375 or multiplying it by 2·67.[1] Thus if a coffee-infusion have a density of 1009·0, the proportion of matter soluble in water will be

$$\frac{1009\cdot0 - 1000\cdot0}{0\cdot375} = 24\cdot0 \text{ per cent.}$$

The figures for soluble extract obtained by T. Macfarlane (Ottawa) by the analysis of 54 samples of commercial coffee ranged from 21·5 to 26·5 per cent., with an average of about 24 per cent.[2] The samples were dried at 100°, deprived of fat by treatment with petroleum ether, re-weighed, and then exhausted with water. Instead of evaporating the infusion and weighing the soluble extract, the insoluble residue was dried and weighed, and the loss gave the soluble extract. A. Smetham has also proposed to wash, dry, and weigh the insoluble matter left on the filter.

Alfred E. Johnson states the soluble extract from previously dried (roasted) coffee to be very constant at 24 per cent., and the extract from dried chicory to average 70 per cent.,[3] and on these figures bases the following process for the analysis of coffee mixtures.

The ground coffee is dried at 100° C. and 5 grammes weight of the moisture-free sample boiled for fifteen minutes with 200 c.c. of water. After settling for a few minutes, the liquid is poured off through copper wire-gauze or coarse muslin into a 250 c.c. flask. The grounds are boiled with 50 c.c. of water for five minutes and the liquid strained as before. The contents of the flask are cooled, made up to 250 c.c., agitated, and poured on to a dry filter. Fifty c.c. of the filtrate, rejecting the first portion (equal to 1 gramme of the dry sample), is then evaporated in a flat dish over boiling water,

[1] This factor is deduced from the known solution-densities of caramel and the carbohydrates. J. Skalweit (*Rep. Anal. Chem.*, 1882, page 227), as the result of direct experiment, gives the following data:—

At 17·5° C.,	1·001 sp. gr.	of 20 % infusion	represents	0·36	extract	per 100 c.c.
,,	1·115	,,	,,	27·24	,,	,
,,	1·235	,,	,,	48·25	,,	,,

[2] The purity of some of these samples was doubted, and Macfarlane considers 22·0 per cent. to represent more accurately the usual proportion of extract yielded by genuine coffee.

[3] O. Hehner found a lightly-roasted chicory (dried) to give 67·1 per cent. of soluble matter, and an infusion-density of 1024·4, while a highly-roasted sample had an infusion-density of 1019, and yielded only 54·1 per cent. of extract.

and the residue (representing the extract from 1 gramme) dried in the water-oven and weighed. Then:—

$$\frac{100\,(70 - \text{per cent. of extract found})}{46} = \text{percentage of coffee in sample.}$$

The results thus yielded by coffee and its principal adulterants are given on pages 543, 544.

The tinctorial power of the infusion was suggested by Graham, Stenhouse and Campbell (*Jour. Chem. Soc.*, ix. 36) as a means of determining adulterants in coffee. They found that the depth of colour of the liquid obtained by infusing coffee and its adulterants in 2000 times their weight of boiling water varied remarkably, caramel giving about seven times and chicory about three times as deep a colour as coffee.[1] But their experiments showed that four different samples of pure coffee varied in tinctorial power between 143 and 183, as compared with caramel as 1000, and no doubt samples of chicory would be found to present at least as great difference in colouring power, according as they happened to be lightly or strongly roasted. Nevertheless the author found (*Chem. News*, xxix. 140) that the tinctorial power of an infusion of mixed samples of chicory was almost exactly three times that of an infusion of average or mixed coffee, and that different samples of chicory did not vary more than from 2·8 to 3·2 in colouring power when compared with the same sample of coffee. In order to estimate the proportion of chicory in a sample of coffee mixture, a standard mixture should be prepared by mixing together several representative samples of genuine ground coffee with an equal weight of mixed chicory.[2] One gramme of this standard coffee mixture (containing 50 per cent. of coffee), and the same weight of the sample to be tested, are boiled for a few minutes with 20 c.c.

[1] The following are the relative amounts of various roasted substances found by Graham, Stenhouse, and Campbell to impart an equal depth of colour to the infusion:—

Caramel,	1·00	Parsnips,	2·50	Coffee,	5·46 to 6·95
Mangold wurzel,	1·66	Maize and rye,	2·86	White lupin-seed,	10·00
Black malt,	1·82	Dandelion root,	3·33	Beans and peas,	13·33
White turnips,	2·00	Red beet,	3·33	Spent tan,	33·00
Carrots,	2·00	Bread raspings,	3·64	Brown malt,	40·00
Chicory (darkest Yorks),	2·22	Acorns,	5·00		

[2] If the standard coffee mixture be kept, it undergoes a change which modifies, even in a dry state, the colour of the infusion. A permanent standard of the right tint can be made by mixing solutions of ferric, cobalt, and copper sulphates in proper proportions. The yellowish-brown glass employed in Lovibond's tintometer for the colorimetric determination of carbon in steel can also be employed as a standard, if its value be previously ascertained. The tints are best observed by placing a piece of wet filter-paper behind the tubes while they are held up to the light.

of water. The liquids are cooled and passed through a double filter, the insoluble portions being repeatedly boiled with fresh quantities of water till no more colour is extracted. The solution of the standard mixture is then made up with water to 200 c.c., and the solution of the sample to 100 c.c. Ten c.c. of this latter liquid is poured into a narrow graduated tube, and some of the standard solution into another tube of exactly equal bore. If the sample consists of pure coffee, the two liquids will now be of exactly similar tint; but if chicory be present, the solution of the sample will be the darker, in which case water is gradually added till the tints are precisely equal. When this point is attained, the volume of the sample solution is observed. Every 1 c.c. of water added represents 5 per cent. of chicory in the sample. Thus if the liquid measure 17 c.c., the sample contains 35 per cent. of chicory.

J. R. Leebody (*Chem. News*, xxx. 243) has described a similar method, but, instead of observing the colour of the solutions transversely, he dilutes the solution from 1 gramme of the coffee to 700 c.c. and observes the colour from above, as in nesslerising water.

The observation of the infusion-colour is occasionally very useful as an indication of the presence of caramel added as such, since in that case the colour will be greatly in excess of the proportion of chicory or other adulterant as deduced by other methods.

The *caffeine* of coffee is tolerably constant in amount, and hence its determination has been recommended by Paul and Cownley (*Pharm. Jour.*, [3], xvii. 565, 648, 821, 921) as means of estimating the proportion of real coffee in a mixture. These chemists have shown (page 492) that most of the published methods for the determination of caffeine give results more or less below the truth, but that when the process recommended by them is adopted the proportion of caffeine isolated varies within comparatively narrow limits. This is especially the case if the roasted berries are dried at 100° before grinding them, as by this means the error due to variable proportions of water is eliminated, and the coffee can be obtained in a finer state of division, and hence be more perfectly exhausted. In fourteen commercial samples of coffee-berries, Paul and Cownley found the moisture to vary from 6·2 to 10·0 per cent. After drying at 100° C. the caffeine ranged from 1·20 (in a coffee from Coorg) to 1·29 per cent. (found in coffee from several sources), except in Liberian coffee, which yielded 1·39 per cent. On the basis of 1·3 per cent. of caffeine in genuine coffee, adopted by Paul and Cownley, the proportion of real coffee in a mixture will be found by dividing the percentage of alkaloid found into 130. It would be safer to adopt the number 120 instead of 130, and in using the method great care is necessary to effect the isolation of

the whole of the caffeine. To ensure this, the sample must be in very fine powder, the exhaustion by alcohol of the mixture of coffee with lime or magnesia must be *proved* to be complete, and the agitation of the aqueous liquid with chloroform must be repeated until no more alkaloid is extracted.

Although, when taken alone, any one of the foregoing methods of examining coffee is liable to lead to determinations of the proportion of adulterants somewhat wide of the truth, by the combined use of several a fairly accurate deduction can be made. In certain rare cases, additional information may be obtained from the determination of the fatty matters, the alkalinity of the soluble ash, and the proportion of nitrogen.

COFFEE EXTRACTS are prepared with very limited success by subjecting roasted coffee to treatment with boiling water or steam, and adding the volatile products to the aqueous extract. The product is deficient in caffeine, and does not contain all the extractive matter of the coffee; nor, when diluted with the appropriate amount of water, is the colour the same as that of the freshly-prepared liquid. To remedy this defect caramel is added, together with strong alcohol as a preservative. In one patent, addition of chicory and sugar is prescribed. The following results were obtained by A. Domergue by the examination of six samples of coffee extract:—

	Water.	Extract dried at 100° C.	Caffeine.	Ash.
A, . . .	86·3	13·7 per cent.	0·106 per cent.	0·61 per cent.
B, . . .	82·4	17·6 ,,	0·105 ,,	0·79 ,,
C, . . .	58·99	41·01 ,,	0·060 ,,	4·30 ,,
D, . . .	72·8	27·2 ,,	0·040 ,,	3·10 ,,
E, . . .	69·9	30·1 ,,	0·050 ,,	1·40 ,,
F, . . .	80·74	19·26 ,,	0·096 ,,	1·83 ,,

Samples A and B were prepared in the laboratory. C, D, and E were coloured with caramel. Domergue regards the proportion of caffeine as the best indication of the value of a coffee extract.

Of three samples of "coffee extract" examined by G. L. Spencer, one was destitute of caffeine, but contained cereals and other starchy bodies; a second contained 1·19 per cent. of caffeine, or about as much as ordinary coffee; and a third was a mixture of coffee extract with milk and sugar, and contained 0·72 per cent. of caffeine. Very notable proportions of tin and copper were detected in these preparations.

Kola-nuts.[1]

The Gourou or Kola-nut, from a tree belonging to the family *Sterculiaceæ*, is chewed and used for preparing a beverage in Western Africa, by the negro inhabitants of the West Indies, Brazil, &c.

From the nut of *Sterculia* or *Cola acuminata*, the female or true Kola, Heckel and Schlagdenhauffen (*Pharm. Jour.*, [3], xiv. 584) obtained the following products:—

Extracted by Chloroform:—	Caffeine,	2·348	per cent.
	Theobromine,	0·023	,,
	Fats,	0·585	,,
	Tannin,	0·027	,,
Extracted by Alcohol:—	Tannin,	1·591	,,
	Kola red,	1·291	,,
	Glucose,	2·875	,,
	Salts,	0·070	,,
Undissolved:—	Starch,	33·754	,,
	Gum,	3·040	,,
	Colouring matters,	2·561	,,
	Proteids,	6·761	,,
	Cellulose,	29·830	,,
	Ash,	3·325	,,
	Water,	11·919	,,

According to E. Knebel (*Apoth. Zeit.*, 1892, p. 112), kola-nuts contain a glucoside, kolanin, which on boiling with water, or by treatment with dilute acids, splits up into caffeine, glucose, and kola-red, $C_{14}H_{13}(OH)_5$. This last product is an extremely unstable substance, taking up oxygen during the drying of the nuts, with separation of water and formation of gallotannic acid, $C_{14}H_{10}O_9$. It is stated that fresh kola-nuts have a greater physiological activity than when dried, as in the former condition the kolanin has not undergone the degeneration which destroys it and renders the caffeine insoluble.

Monaron and Perrone state that powder and extract of kola-nuts have a far greater power of diminishing the elimination of phosphates and nitrogen than caffeine alone has. Kola-red has

[1] Kola-nuts are oblong, three forming a ball fully 2 inches in diameter, and resembling a very large horse-chestnut. The individual nuts have a rugged, dark brown surface. Inside they are light brown, becoming rusty on exposure, and tough as wood. When fresh the taste is first sweet, then astringent, and finally bitter. After drying the bitterness diminishes.

Various other African plants yield seeds closely resembling the true Kola, but it is doubtful whether they contain caffeine.

a diminishing influence, but both it and caffeine act better in their natural combination than separately. Caffeine has a diuretic action, whereas kola is anuretic. The drug prevents waste of brain as well as of muscular tissue.

FALSE KOLA, MALE KOLA, or KOLA BITTER, is the seed of *Garcinea kola*, a plant of the family of the *Guttiferæ* growing in Liberia and Central Africa. On extracting the seeds with chloroform, ether, and alcohol, no caffeine is obtained, but only resins. One of these gives a violet coloration with ferric salts, while the other is dextro-rotatory and precipitated by tartar emetic and basic lead acetate. The physiological action of the extract of kola bitter is attributable to these resins.

Guarana.[1]

This product occurs in the form of cylinders. It is an indefinite mixture of various materials, of which the seeds of *Paullinia sorbilis* appear to be the only constant and characteristic ingredient. It is prepared by the Guaranis, a tribe of half-savage Indians on the Upper Amazon. Its only interest is as a source of caffeine, of which it contains a notable proportion. Stenhouse obtained 5·04, and F. V. Green 5·05 per cent. E. R. Squibb found 4·83 per cent. (*Ephemeris*, ii. 615). J. H. Feemster (*Pharm. Jour.*, [3], xiii. 363) obtained from 3·9 to 5·0 per cent. of caffeine from five samples of guarana. The alkaloid is readily isolated in a state of purity by boiling the substance with water and litharge for some hours, or until the liquid is colourless and the deposit settles readily, concentrating the filtered liquid, and agitating with chloroform.

Cocoa and Chocolate.

Cocoa is the seed of the tree *Theobroma cacao* and allied species growing wild in tropical America. It is cultivated in Brazil, Grenada, Trinidad, &c., and has been introduced into the East Indies and parts of Africa and Australia. The cocoa-seeds from different districts vary considerably in appearance and flavour, but do not present any sharp distinctions in chemical composition.

The fruit of the cocoa contains from 25 to 40 seeds closely packed in the pulp, which is removed by subjecting the seeds to a process of fermentation for a few days. The pulp is then separated by hand, and the seeds placed in trays and dried slowly in the sun or by artificial heat, being turned over at intervals. The flavour

[1] Throughout Brazil, and in all parts of South America where the preparation is used, the word guaranâ is universally accented on the last syllable, and never pronounced guarâna.

J. Bell (*Analysis and Adulteration of Foods*) gives the following particulars respecting the composition and the *ash* of cocoa-nibs and husk:—

Kind of Cocoa.	Per 100 Parts of Cocoa.			Per 100 Parts of Ash.					
	Moisture.	Alkaloid.	Ash on Dry Substance.	Soluble in Water.	Insol. in Acid.	P_2O_5.	CO_2.	K_2O.	FeO.
Guayaquil nibs,	5·06	0·54	3·63	56·20	none	49·39	0·69	23·35	0·21
Surinam nibs,	4·55	0·80	2·90	43·45	none	37·78	3·31	28·00	0·38
Grenada nibs,	5·71	0·91	2·82	48·58	none	39·20	2·92	27·64	0·15
Finest Trinidad nibs,	4·47	0·84	2·75	46·55	none	36·20	4·19	29·30	0·11
„ „ husks,	10·19	1·35	8·63	54·92	5·91	17·17	10·80	37·89	0·63

In these analyses the figures for alkaloid are probably considerably below the truth.

The *ash* of cocoa is distinguished by the small proportion of chlorides, carbonates, and sodium compounds contained in it, and by the great preponderance (3 or 5 : 1) of magnesia over lime.

In Bell's analyses of cocoa-ash, no mention is made of the presence of copper. Duclaux proved this metal to be constantly present in cocoa. Galippe confirmed this, and found proportions varying from 0·0112 to 0·0292 grammes per kilogramme of cocoa. The greater part of the copper existed in the husks, and in inferior kinds of chocolate containing cocoa-husk in large proportion copper was occasionally present to the extent of 0·125 gramme per kilogramme.

The most important and characteristic constituent of cocoa is the alkaloid *theobromine*. A small proportion of caffeine is sometimes present in addition. The recorded proportions of theobromine are very variable and generally untrustworthy. The method of determination has already been described (page 496). P. Troganowski (*Archiv der Pharm.*, [3], x. 32; *Jour. Chem. Soc.*, xxxii. 363) found from 1·2 to 4·6 per cent. of theobromine in cocoa, and concluded, from the result of a large number of experiments, that the proportion of alkaloid does not always bear a relation to the quality and value of the cocoa. This is probable, but the difficulty attending the accurate determination of theo-bromine in cocoa renders any deduction of the kind of very doubtful value.

The *fat* of cocoa (*Oleum Theobromatis*, B.P.), sometimes called "cocoa butter," consists chiefly of stearin, and is fully

described on page 568. The proportion of fat present in cocoa-nibs, free from husk, varies only a few units on each side of 50 per cent., and hence is valueless for the discrimination of samples from different sources.

The taste and aroma of cocoa are chiefly due to a volatile substance, probably an essential oil, which appears to be developed by roasting, in the same manner as the caffeol of coffee (page 532). The *tannin* of cocoa also contributes to the flavour.

The *cocoa-red* probably does not pre-exist in cocoa, but is a product of the oxidation of the tannin. If cocoa, from which the fat has been previously removed (by petroleum spirit), be exhausted with alcohol, and the solution treated with acetate of lead, a precipitate is produced, which, when suspended in water and decomposed by sulphuretted hydrogen, yields a clear and colourless filtrate; but on evaporating this liquid, it acquires a bright red colour, and on taking up the residue with water, cocoa-red remains insoluble. Cocoa-red gives various coloured precipitates with metallic salts, the tints depending on the extent to which oxidation has occurred, and, apparently, on the variety of cocoa employed. P. Troganowski (*Archiv. der Pharm.*, [3], x. 32; *Jour. Chem. Soc.*, xxxii. 363) has described various colour-reactions yielded by the aqueous or alcoholic solutions of cocoa from various sources, but the value of the indications obtained is very questionable.

The *gum* of cocoa closely resembles gum-arabic in appearance, and yields mucic acid on oxidation with nitric acid. It differs from gum-arabic in being strongly *dextro*-rotatory.

The *starch* of cocoa is present in only moderate proportion, and the amounts recorded by some observers are probably in excess of the truth. The granules are small, round, and exhibit a central hilum. Under the microscope they are readily distinguished from the granules of added starches.

Nitrogenous constituents of cocoa. G. W. Wigner (1878) showed that of the nitrogen of cocoa only a portion varying from 39 to 78 per cent. existed in a coagulable form (*Analyst*, iv. 8). The total nitrogen, as determined by combustion with soda-lime, ranged from 0·70 to 2·98 per cent., and that existing as coagulable albuminoids from 0·33 to 2·33 per cent. According to Wigner, of the nitrogen in a non-coagulable form, part exists as theobromine and a further portion as nitrates. Wigner argued from this that the value of cocoa as food had been over-estimated.

Weigmann similarly found only 42 per cent. of the nitrogenous substances in cocoa to be digestible; and Stutzer states that, in spite of apparently favourable conditions, due to the physical condition of commercial cocoa, a large proportion of the

nitrogenous constituents remains entirely indigestible. Stutzer classifies the nitrogenised compounds of cocoa as follows:—1. Non-proteids; substances soluble in neutral aqueous solution in presence of cupric hydroxide (theobromine, ammonia, amido-compounds). 2. Digestible albumin; insoluble in neutral aqueous solutions in presence of cupric hydroxide, but soluble when treated successively with acid gastric juice and alkaline pancreas extract. 3. Insoluble and indigestible nitrogenous substances.

The following are the results of the analysis of four cocoa powders examined by Stutzer (*Zeitsch. f. angew. Chem.*, 1891, page 368) for the purpose of determining the effect of the process of manufacture on the chemical constituents. A was composed of 40 per cent. Ariba, 40 of Machala, and 20 of Bahia cocoa, and was manufactured by Wittekop & Co. without the use of chemicals. B is a sample of a well-known cocoa manufactured in Holland with the addition of potash.[1] C and D are German cocoas, and, in Stutzer's opinion, were prepared by the use of ammonia:—

	A.	B.[1]	C.	D.
	Per cent.	*Per cent.*	*Per cent.*	*Per cent.*
Water,	4·30	3·83	6·56	5·41
Fibre,	3·36 }	37·48	39·99	36·06
Nitrogen-free extract,	38·62 }			
Total nitrogenous substances,[1]	20·84	19·88	20·93	19·25
Fat,	27·83	30·51	27·34	33·85
Ash,[2]	5·05	8·30	5·18	5·43
	100·00	100·00	100·00	100·00
[1] Containing total nitrogen,	3·68	3·30	3·95	3·57
Composed of:—				
Theobromine,	1·92	1·73	1·98	1·80
Ammonia,	0·06	0·03	0·46	0·33
Amido-compounds,	1·43	1·25	0·31	1·31
Digestible albumin,	10·25	7·68	10·50	7·81
Indigestible nitrogenous substances,	7·18	9·19	7·68	8·00
Containing nitrogen,	1·15	1·47	1·23	1·28
Proportion of total nitrogen indigestible,	31·2	44·5	31·2	35·8
[2] Containing:—Total P_2O_5,	1·85	2·52	2·14	2·05
P_2O_5 soluble in water,	1·43	0·50	0·74	0·77
Ratio of *total* P_2O_5 to *soluble*,	100 : 77	100 : 19	100 : 34	100 : 37
Ash soluble in water,	3·76	4·76	2·82	2·76
Ratio of *total* ash to *soluble*,	100 : 74	100 : 57	100 : 54	100 : 49

[1] An analysis of the ash of Van Houten's cocoa by König (in 1880) showed:—Total ash, 7·84; K_2O, 3·52; CaO, 0·27; MgO, 0·81; P_2O_5, 1·84

COMMERCIAL COCOA AND CHOCOLATE.

In its simplest form, commercial cocoa consists of the roasted and husked seeds ("nibs") ground to a paste or semi-fluid, and run into the form of cakes. *Flake cocoa* is sometimes made by passing the decorticated seeds through a particular kind of rollers but it is mostly made from the small particles containing much shell and germ, separated by the sieves.

The term "cocoa" is sometimes misapplied to mixtures of real cocoa with sugar, &c. The practice is highly objectionable and has led to much confusion. It is better to describe all such cocoa mixtures as *chocolate*, reserving the name cocoa for the unmixed article.

All good cocoa preparations should be made from the cotyledons only, though the husks enter into the composition of many of the inferior kinds of cocoa and chocolate. In Germany, under the name of "cocoa-tea," and in Ireland as "miserables," cocoa-husks are an independent article of commerce,[1] the infusion of which in boiling water is drunk after the manner of tea.

The large proportion of fat in cocoa (averaging 50 per cent.) renders it impossible to manufacture a permanent preparation in the form of powder, without either removing a portion of the fat or diluting the material with some non-fatty matter, such as sugar, starch, or farina. Hence, there are two distinct types of "cocoa" known in commerce, namely :—

1. Preparations commonly called "cocoa-essence," or "cocoa-extract," consisting of ground cocoa-nibs, from which a part of the fat has been removed by heat and pressure.

2. Preparations to which sugar and, generally, some starchy material have been added. The *sugar* is usually sucrose (cane or beet sugar), but reducing sugars are sometimes present in notable quantity. Of the pure starches, arrowroot and rice starch are used in the better preparations, while wheat- and potato-starches and wheat-flour are also met with. Moeller also mentions acorn and rye flours, ground earth-nuts, and malt, to which Macé adds almond-cake and sawdust. Any cheap vegetable material, capable of being reduced to fine powder, is liable to be used by unscrupulous

per cent. Belohubeck (in 1888) found :—Total ash, 7·88 ; and for 100 of total ash, K_2O, 52·89 ; CaO, 1·56 ; MgO, 10·45 ; P_2O_5, 24·91 ; CO_2, 3·45 per cent.

[1] In large cocoa manufactories the husks are sorted by sieves into several sizes. The largest are employed for infusion, and the finest, containing a considerable admixture of the kernels, are ground up with sugar and cacao-butter to produce a low grade of chocolate. The intermediate sizes are not readily applicable for either of the above purposes, and hence fetch a lower price than the coarsest and finest husks. They are employed for cattle-food, and at Hamburg are pressed for the extraction of cacao-butter.

cocoa manufacturers, but the better class of preparations which have acquired a reputation in the United Kingdom are free from any suspicion of such admixtures.

A considerable addition of cacao-butter is made to some kinds of chocolate.[1]

The *flavouring agents* added to chocolate are most frequently vanilla and cinnamon. Artificial vanillin, nutmeg, cloves, mace, &c., are also used. In addition to the mechanical difficulty of manipulating undiluted cocoa containing all its natural fat, it is stated, with some probability, that the excessive proportion of fat renders the cocoa difficult of digestion. Hence the removal of a portion of the fat, and consequent concentration of the non-fatty constituents of the cocoa, appears to be distinctly advantageous.

A further treatment of the concentrated cocoa is practised by some manufacturers of cocoa-essence, especially by Dutch firms. This treatment consists in the addition to the cocoa of an alkali, which may be either ammonia or a fixed alkali or alkaline carbonate, whereby the fat becomes emulsified and any free fatty acids saponified. Hence, on subsequently treating the cocoa with hot water there is less tendency to the separation of oily globules. The effect on the composition of the cocoa is shown in the results of Stutzer on page 560, from which it appears that the fact of the treatment can be readily detected. In the case of a well-known brand of cocoa, potassium carbonate is used. In another case, the cocoa-beans are soaked in water containing from 2 to 4 per cent. of their weight of caustic potash or soda.

The following figures were obtained by the analysis, in the author's laboratory, of a specimen of the best cocoa-nibs and two of the leading brands of cocoa-essence or soluble cocoa, to which no starch or sugar had been added:—

	Cocoa-nibs.	Sample A.	Sample B.
	Per cent.	Per cent.	Per cent.
ASH:—	2·53	4·93	8·25
Insoluble in water,	1·71	3·50	2·09
Soluble in water,	0·82	1·43	6·16
Alkalinity (K_2O) of soluble portion,	0·32	0·49	3·23
COLD WATER EXTRACT:—	9·72	11·64	18·66
Alkalinity (K_2O) to methyl-orange,	0·69	0·71	2·02
Acidity (K_2O) to phenolphthalein,	0·63	0·76	0·38
HOT WATER EXTRACT:—	16·84	20·36	27·16
Containing:—Ash,	3·34	4·93	7·85
Organic extract,	13·50	15·43	19·31

[1] "Chocolate creams" consist of a core or kernel of pure sugar, enveloped in a mixture of ground cocoa, cacao-butter, sugar, and flavouring materials.

The curious property possessed by the cold-water extract of being at once alkaline to methyl-orange and acid to phenolphthaleïn indicates the presence of a soluble salt of some weak organic acid, together with a small proportion of free organic acid. The treatment with alkali which sample B had received appears to have notably increased the proportion of matter actually soluble in water.

The misuse of the term "soluble" by cocoa manufacturers is notorious; the real object sought, and to some extent attained, being the formation of an emulsion which is readily miscible with hot water. This desideratum is the more important owing to the difficult digestibility of some of the nitrogenous constituents of cocoa (see page 559).

The following results, among many others, were obtained by E. E. Ewell (*Bulletin* No. 13, U.S. Department of Agriculture) by the analysis of well-known brands of commercial cocoa and its preparations :—

Description of Sample.	Husk.[1]	Fat.	Fibre.	Cane-sugar.	Reducing Sugar.	Ash. Total.	Ash. Acid-equivalent.[2]	Added Starch.
Fry's Cocoa Extract .	1	30·95	3·89	...	...	4·24	5·8	None.
Schweitzer's Cocoatina,	1	31·13	3·70	...	...	6·33	9·4	None.
Van Houten's Cocoa, .	1	29·81	4·38	...	...	8·64	16·05	None.
Blooker's Dutch Cocoa,	0	31·48	3·76	...	...	6·06	9·6	None.
Rowntree's Extract of Cocoa, . .	2	27·56	4·42	...	...	8·48	16·6	None.
Rowntree's Powdered Chocolate, . .	2	25·84	1·30	51	none	1·66	2·25	Very small amount of arrowroot.
Epps' Prepared Cocoa,	...	25·94	1·51	26	none	3·15	2·6	Much arrowroot.
Fry's Diamond Sweet Chocolate, . .	2	18·60	·81	55	some	1·16	1·45	Much wheat-starch with some arrowroot.
London Cocoa (unknown maker), .	3	11·13	2·13	32	some	2·82	3·9	Very largely diluted with arrowroot.
Chocolat-Menier, .	0	21·31	1·10	58	none	1·40	2·05	None.

[1] In the column headed "husk," 0 signifies that no characteristic husk-tissue could be found under the microscope; 1 signifies that the husk had probably been mostly removed; 2 signifies that the husk had probably been partly removed; and 3 that the husk was probably all present. But Ewell's observations with respect to the husk of commercial cocoas are not in all cases borne out by the examination of other samples of the same preparations, and must be received with caution.

[2] The figures in the column headed "acid-equivalent" represent the number of c.c. of decinormal acid required to neutralise the ash from 2 grammes of the sample. It is a rough measure of the fixed alkali used in the manufacture.

Owing to a considerable proportion of the natural fat having frequently been removed, the proportion of real cocoa in a mixture cannot be assumed to be approximately double the percentage of fat. A better idea of the proportion of the additions is obtained by stating the fat and non-fatty constituents separately. This plan is adopted by J. Bell, and is shown in the following analyses by him, representing the composition of certain commercial preparations of cocoa:—

Description.	Moisture.	Fat.	Added Sugar.	Added Starch.	Non-fatty Cocoa (by difference).	Nitrogen.
Finest Trinidad nibs, .	2·60	51·77	none	none	45·63	2·95
Cocoa Extract, . .	5·76	29·50	none	none	64·74	Not determined.
Flake Cocoa, . . .	5·49	28·24	none	none	66·27	3·06
Cocoatina, . . .	3·52	23·98	none	none	72·50	4·07
Chocolatine, . . .	4·40	29·60	none	none	66·00	4·36
Chocolat de Santé, .	1·44	22·08	61·21	2·00	13·27	Not determined.
Prepared Cocoa, . .	4·95	24·94	23·03	19·19	27·89	2·24
Iceland Moss Cocoa, .	5·47	16·86	29·23	24·70	23·74	1·38
Rock Cocoa, . . .	2·58	22·76	32·20	17·56	24·90	Not determined.

According to evidence given in the case of Gibson *v.* Leaper, "Epps' cocoa" contains 40 per cent. of cocoa, 16 of starch (West Indian arrowroot), and 44 per cent. of sugar. "Granulated cocoa" is chiefly a mixture of cocoa-nibs, sugar, and arrowroot; while in "Maravilla cocoa" the arrowroot is replaced by sago. Bernhardt states that he has met with chocolates consisting of cocoa-remnants, fat, sugar, spices and colouring matter, and containing no true cocoa whatever. The cocoa-butter is said to be liable to be replaced by cheaper fats, and vanilla and vanillin by Peruvian or Tolu balsam, storax, or gum benzoïn.

Analysis of Commercial Cocoa and Chocolate.

The complete analysis of cocoa is rarely required. A careful microscopic examination will indicate the presence, and in many cases the nature, of most foreign additions, and prove the presence of husk-structure. The various starches may also be identified by the microscope. The proportion of fat affords further information, and the percentages of sugar and starch complete what is usually required, unless it is desired to ascertain the nature and amount of the alkali added. The following scheme of analysis will allow of the above information being obtained:—

Ignite 5 grammes of the sample, weigh the *ash* and treat with boiling water. Wash, dry, ignite, and weigh the *insoluble* portion. Titrate the filtrate with decinormal acid to determine the *alkalinity*, which will be excessive where the cocoa has been prepared with a fixed alkali. The addition to cocoa of ferruginous pigments, such as rouge, ochre, and venetian-red, was formerly practised, and the author was recently consulted as to the probable legal consequences of their use. He has also examined a preparation consisting essentially of oxide of iron, which has recently been offered to cocoa-manufacturers. Where the proportion of the diluents is large, the importance of deepening the colour of the mixture is considerable. The addition of ferruginous matters would be readily detected by the excessive proportion of the ash, which in the case of genuine cocoa is white, and very rarely in excess of 4 per cent. (in the absence of husk and added alkalies, and when the fat has not been removed). The proportion of oxide of iron in cocoa is very trifling, ranging from 0·10 to 0·38 per cent. *of the ash*, while even in the husk it only amounts to 0·63 per cent. of the ash.

Dry 5 grammes of the sample in the water-oven at 100° C. and note the loss of weight, which represents *moisture*. Boil the dried substance, reduced to powder if necessary and preferably mixed with a known weight of dry sand, with redistilled petroleum spirit. Pour off the solution, and repeat the treatment till the fat is entirely removed. Wash the residue, dry it in the bath and reweigh. The loss represents *fat*, with a near approach to accuracy. A direct determination may be obtained by evaporating the petroleum spirit, and the physical and chemical characters of the residual fat can then be ascertained.[1]

The residue left after the extraction of the fat is exhausted with hot spirit of 0·850 specific gravity, which dissolves sugar, tartaric acid, tannin, soap, theobromine, &c. The hot solution is treated with lead acetate and filtered from the precipitate of lead *tartrate*, *tannate*, *stearate*, &c. From the concentrated filtrate the *theobromine* can be extracted by agitation with warm chloroform, but where the determination is not required this stage of the process may be omitted. The aqueous liquid is freed from traces of chloroform by boiling or agitation with petroleum spirit, and after removal

[1] Cocoa which has been treated with an alkali contains a notable quantity of *soap*, which is not dissolved by the petroleum ether. It is best extracted by treating the residue with alcohol containing a few drops of hydrochloric acid, evaporating the alcoholic solution, and shaking the residual liquid with water and ether. On separating and evaporating the ethereal layer, the fatty acids of the soap will be left

of the excess of lead by sodium phosphate is fit for determination of the sugar. This may be effected by inversion and treatment with Fehling's solution, or by means of the polarimeter. The difference in the amount of sugar found before and after inversion represents the *cane-sugar* added. The alcoholic extract of genuine cocoa, after treatment with lead acetate, does not sensibly reduce Fehling's solution, so that any precipitate yielded before inversion represents *glucose*, introduced as such or present in the cane-sugar added.[1]

The residue left after treatment with alcohol contains gum, starch, cellulose, fibre, albuminoid matters, &c. After weighing, an aliquot part may, if desired, be used for the determination of the contained nitrogen by Kjeldahl's process or combustion with soda-lime, and the amount found calculated to *albuminoids* by multiplying by 6·25. The residue may also be advantageously examined under the microscope at this stage, since by the removal of the oil, sugar, and colouring matters the starch and woody structure are seen to great advantage. On the presence or absence of foreign starch will usually depend the necessity of performing the subsequent operations for its quantitative determination.

For the determination of *starch*, an aliquot part of the residue from the alcohol treatment[2] should be heated, under a pressure of

[1] A determination of the amount of sugar added to cocoa can be readily effected to within 2 per cent. of the truth, but a strictly accurate estimation is not required, and would be very difficult. The sugar can be determined in the aqueous instead of the alcoholic extract of the cocoa, but in that case the solution contains the natural gum, which has a dextro-rotatory power equivalent to 0·3 to 2·0 per cent. of cane-sugar in the sample, and a large volume of cold water must be used for the extraction. E. E. Ewell (*Bulletin* No. 13, U.S. Department of Agriculture) recommends the following method for the polarimetric determination of sugar in the aqueous extract of cocoa :—13·024 grammes weight of the material is triturated in a small mortar with alcohol until a smooth paste is obtained. This is transferred to a 500 c.c. flask, diluted with about 400 c.c. of water, and the liquid shaken occasionally for three or four hours, when 10 c.c. of a saturated solution of neutral lead acetate should be added and the volume brought to 500 c.c. After standing for an hour with occasional agitation, the solution is filtered and polarised in a 4 decimetre tube (twice the usual length). If the instrument be one intended for use with 26·048 grammes of sugar, the percentage of cane-sugar in the sample will be found by the following formula, in which R is the reading in sugar-units :—

$$\frac{R}{100}\left[500-(13{\cdot}024)-\frac{5R\times 13{\cdot}024}{100}\right]=\text{per cent. of sucrose.}$$

[2] The residue is preferably first treated with cold water, to dissolve gummy matters, but except in cases where great accuracy is required this part of the process may be omitted.

1 atmosphere, for one hour with 50 c.c. of water and 1 c.c. of fuming hydrochloric acid.[1] This treatment effects the complete conversion of the starch into maltose and dextrin, and the further change of these to dextrose, without appreciably affecting the cellulose. The solution is filtered from the insoluble matter, fibre (sand), &c., and the dextrose determined in the neutralised filtrate by Fehling's solution. Ten parts of dextrose found represent 9 of starch in the sample.

The mixed *cellulose*, *fibre*, and sand, left after the conversion of the starch by hydrochloric acid, should be treated with a solution of 2 per cent. caustic soda to remove nitrogenous matters, washed successively with very dilute hydrochloric acid, alcohol and ether, dried and weighed.[2]

An alternative method of estimating *starch* consists in treating the fat-free cocoa with cold water, to remove all sugar, gum, &c. The liquid is filtered and the residue washed with decinormal caustic soda (4 grammes NaHO per litre) to remove albuminoids. The residue is rinsed off the filter with warm water, the liquid heated to boiling while constantly stirred, so as to gelatinise the starch, and the product treated with a known measure of recently-prepared and filtered cold aqueous infusion of malt, of which the specific gravity has been previously ascertained. The mixture is kept at a temperature of 60° to 63°, with occasional stirring, until a drop taken out with a glass rod and added to a drop of dilute iodine solution on a porcelain plate shows no blue or brown coloration. The solution is then filtered, made up to a definite volume,

[1] A simple and convenient apparatus for effecting the conversion consists of a soda-water bottle fitted with an india-rubber stopper, through which passes a long glass tube bent twice at right angles and immersed to a depth of 30 inches in mercury contained in a long vertical glass tube or piece of narrow (iron) gas-pipe. The stopper should be carefully secured by wire. The soda-water bottle may be heated in a bath of paraffin or oil, or in a boiling saturated aqueous solution of sodium nitrate. This last liquid has a temperature of 121° C., corresponding to one additional atmosphere of pressure, so that no regulation is required, and if preferred the exit-tube may be dispensed with and the cork or stopper firmly secured in position.

[2] For the direct determination of the *crude fibre*, 2 grammes of the sample of cocoa should be freed from fat and boiled for half an hour under a reflux condenser with 200 c.c. of water and 2½ c.c. of sulphuric acid. The liquid is filtered through linen and the residue thoroughly washed with hot water and then boiled with 200 c.c. of 1¼ per cent. caustic soda. The residue is filtered off, washed in succession with hot water, alcohol, and ether, dried at 110°, and weighed. It is then ignited, and the loss regarded as *crude fibre*. In cocoa free from husk it will amount to 2 or 3 per cent. only, but will exceed this limit in proportion to the amount of *husk* present.

and its specific gravity accurately ascertained. From the excess of the density over water is subtracted the density due to the infusion of malt used, allowance being made for the increased volume of the liquid, when the difference represents the density due to the starch dissolved, and this number divided by 4·096 (= 3·95, the density-coefficient of a solution of mixed maltose and dextrin, multiplied by 1·037, the yield of these from 1 part of starch) gives the number of grammes of starch in each 100 c.c. of the solution.[1]

The *total nitrogen* of cocoa can be determined on 2 to 3 grammes by Kjeldahl's method, or by combustion with soda-lime. The assumption that the proportion of albuminoids can be found by multiplying the nitrogen by 6·25 leads to an estimate greatly in excess of the truth. The theobromine of cocoa contains 31·1 per cent. of nitrogen, or nearly twice as much as albumin. Hence to obtain an estimate of proteids from the nitrogen of the sample, the proportion of that element corresponding to the theobromine present must first be deducted. But as the determination of theobromine is somewhat troublesome, it is preferable to operate on a cocoa-residue which has been already exhausted with petroleum spirit, alcohol, and amylic alcohol or chloroform, so as to eliminate with certainty the whole of the theobromine.

CACAO-BUTTER (*Oleum Theobromatis*) is the fat contained in cocoa-beans, and must not be confused with c o c o a - n u t o i l from *Cocos nucifera*.

Cacao-butter is expressed from cocoa in the process of manufacture, and by far the larger quantity used in the United Kingdom is the produce of one firm. It is used in pharmacy; for the production of some kinds of chocolate; and in the manufacture of high-class soap. Cacao-butter is liable to adulteration with or substitution by other fats, and it is said that the cacao-butter is sometimes very completely expressed from cocoa and replaced by tallow, cocoa-nut oil, or other comparatively cheap fat.

A careful observation of the physical and chemical characters of

[1] Thus, suppose 20 grammes of the sample of cocoa be taken, and, after extraction of the fat and treatment with cold water and soda in the manner described, the residue be treated with 50 c.c. of water and 5 c.c. of infusion of malt of 1060 specific gravity; the liquid being subsequently made up to 100 c.c. and found to have a density of 1023. Then the correction due to the malt-extract will be $\frac{(1060 - 1000) \times 5}{100} = 3$; and this figure, subtracted from the density of the solution less that of water (1023 − 1000 = 23), leaves 20 as the excess-density caused by the solution of the starch of the sample; and this figure divided by 4·096 gives 4·9 grammes per 100 c.c. or in the 20 grammes taken; or 24·5 per cent. of starch in the sample.

cacao-butter will allow of the detection of other fats, if present in any considerable proportion.

Pure cacao-butter is a yellowish fat, gradually becoming paler on keeping.[1] At the ordinary temperature it may be broken into fragments, but softens in the hand and melts in the mouth. Cacao-butter has an agreeable odour, tastes like chocolate, and does not readily become rancid. It dissolves in 20 parts of hot alcohol, separating almost completely on cooling, and is also soluble in ether, acetic ether, &c.

Cacao-butter owes its value for the production of pessaries and suppositories to the fact of its having a melting-point slightly below the temperature of the human body (98° F. = 36·6° C.). According to most observers, it fuses between 30° and 33° C. (rarely at 26°) to a transparent yellowish liquid, which congeals again at 20°–21°, the temperature rising to about 27° C. According to the *British Pharmacopœia*, the melting-point of cacao-butter ranges between 30° and 35° C. (86°–95° F.).[2]

[1] It is to be regretted that the yellowish tint of cacao-butter is not more generally recognised as a natural characteristic. It is probable that the quality of cacao-butter is necessarily affected for the worse by any process of decolorisation.

[2] R. Bensemann (*Zeit. Anal. Chem.*, xxiv. 628; *Jour. Soc. Chem. Ind.*, iv. 535) has observed the melting-point of cacao-butter and the fatty acids resulting from its saponification, and finds the figures for the latter remarkably constant. He places a drop of the previously-melted fat or fatty acid in the wider part of a piece of quill-tubing drawn out to a capillary form and closed at one end. The substance is allowed to solidify completely, and the tube is then attached to a thermometer and placed in water, which is gradually heated. The temperature at which the substance becomes sufficiently fluid to run down into the capillary part of the tube is called the point of incipient fusion. When the substance has melted and run down into the shoulder of the tube, and shows no trace of turbidity, the temperature recorded is the concluding point of fusion. Bensemann records the following results:—

Source of Cacao-butter.	Fat.	Fatty Acids.		
	Initial Melting-point.	Initial Melting-point.	Concluding Melting-point.	Percentage of Insoluble.
Maracaibo beans,	25–26° C.	48–49° C.	51–52° C.	94·59
Caraccas beans,	27–28	48–49	51–52	95·31
Trinidad beans,	26–27	49–50	52–53	95·65
Portoplata beans,	28–29	49–50	52–53	95·46
Machala Guayaquil beans,	28–29	49–50	52–53	95·24

T. M. Clague has recently pointed out (*Pharm. Jour.*, [3], xxiii. 247) that the melting-point of commercial cacao-butter extends over a considerably greater range than the above, and is materially affected by the temperature to which it has been exposed. Thus, the melting-point of ten trade samples ranged from 73°–91° F. A sample expressed by heat direct from cocoa-nibs melted at 91°, while the fat obtained from the same nibs by extraction with ether melted at 83° F. Similarly, the fat extracted by ether from a "cocoa-essence" had a melting-point of 96°, while the cacao-butter extracted by heat and pressure by the same firm melted at 75° F., *thus showing that a certain amount of fractionation occurs* in the ordinary process of extraction by pressure.

T. M. Clague further observed the following suggestive alterations of melting-point when cacao-butter was heated to various temperatures. Nos. 1 and 2 were ordinary trade samples, and hence had been already heated in the process of manufacture. No. 3 was extracted by ether from unroasted cocoa-nibs, and hence excessive heating had been entirely avoided :—

	Melting-point; ° F.		
	No. 1.	No. 2.	No. 3.
Original,	75	86	86
After being heated to 105° F.,	75·5	89	86
,, ,, 120°,	84	85	91
,, ,, 150°,	85	83	92
,, ,, 180°,	80	80	85

The melting-point of No. 1 sample was raised to 86° F. by keeping it at a temperature just under 100° F. for two hours. The determinations of melting-points were made on metallic mercury, substantially by method *c* described in Vol. II. page 23.[1]

Cacao-butter contains the glycerides of stearic, oleic, and a little lauric, palmitic, and arachidic acids. C. T. Kingzett obtained from cacao-butter an acid of the formula $C_{64}H_{128}O_2$, which he named theobromic acid. P. Graf isolated 9·59 per cent. of glycerol, and detected a little cholesterin and small quantities of formic, acetic, and butyric acids.

[1] T. M. Clague has also described experiments showing that determinations of the melting-point of cacao-butter by the capillary tube method are very gravely affected by the diameter of the tube employed.

The iodine-absorption of a large number of samples of cacao-butter from different sources has been determined by F. Filsinger (*Chem. Zeit.*, xiv. 716), and found to range from 33·4 to 37·5. The saponification-equivalent ranges a few degrees on each side of 280, which figure corresponds to 20·03 per cent. of potash (KHO) required for saponification. Filsinger found the potash required to range from 19·2 to 20·2, and Weigmann from 19·84 to 20·30. An admixture of paraffin wax would reduce the percentage of alkali required for saponification.

The specific gravity of solid cacao-butter is variously stated. The author found the plummet-gravity at 98° C. to be 0·8577. Any admixture of paraffin wax would reduce this figure, while cocoa-nut oil would increase it.

Foreign fats in cacao-butter tend to alter the foregoing characters, but observations of the melting-point and specific gravity do not usually furnish satisfactory means of detecting such admixtures. *Tallow* is said to be capable of detection by saturating a cotton thread with the oil, allowing it to burn for a short time, and then blowing it out, when the odour of tallow becomes perceptible.

A better test for tallow and other adulterants of cacao-butter is to dissolve 2 grammes of the fat in 4 grammes (=5·5 c.c.) of ether at 17°–18° C.,[1] and then immerse the closely-corked test-tube in ice-cold water. Granules will separate from, or turbidity be produced with, pure cacao-butter, in not less than 3 and more frequently in from 5 to 8 minutes, sometimes delayed to 10 or 15 minutes; while if *tallow* or *suet* be present, a turbidity will appear at once, or within 2½ minutes, according to the proportion of the adulterant, of which 5 per cent. may thus be detected. On exposing the solution to a temperature of 14° to 15°, it will gradually become clear again, or more rapidly at 20°, if the cacao-butter was pure, but not if it was adulterated. With a sample containing 5 per cent. of tallow, turbidity occurs in 8 minutes, and the solution does not become clear below 22°; while with 10 per cent. of tallow, the turbidity occurs in 7 minutes, and the clearing-point is 25° C. This test is due to Björkland (*Zeit. Anal. Chem.*, iii. 233), and is adopted in the *United States Pharmacopœia*. Its value has been confirmed by other observers, of whom Lamhofer has pointed out that petroleum-ether may be employed with similar results, except that the cacao-butter separates rather more slowly than from ether, the deposit being always granular, while other fats render the entire liquid cloudy. The solution of cacao-butter in two parts of ether will remain clear for an entire day if maintained

[1] A failure to obtain a clear solution points to the presence of paraffin wax

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ERRATA AND ADDENDA.

VOLUME I.

Page 8, line 9, *for* "multiplied," *read* "divided."
Page 64, column 3, first line of figures, *for* "46·86," *read* "44·86."
Page 304, equation on line 13 *should be* :—

$$S = \cdot 527g + 1\cdot 392m + 1\cdot 98d ; s = 1\cdot 98d.$$

VOLUME II.

Page 68, the saponification-equivalent of palm-nut oil should be "227 to 255."
Page 92, iodine-absorption of nigerseed oil, *for* "103," *read* "133."
Page 136, line 3, *for* "solvents," *read* "selenite."
Page 150, paragraph 5, *for* "85," *read* "80"; and *for* "15," *read* "20."
Page 266, line 11, *for* "alkali," *read* "acid."
Page 267, in foot-note, *for* "8·47," *read* "7·47"; and *for* "64·51," *read* "56·89."
Page 313, line 24, *for* "strong sulphuric acid," *read* "sulphuric acid of 1·76 sp. gravity."
Page 522, in footnote, formulæ of acridine sulphite and nitrate should contain $(C_{13}H_9N)_2$.

VOLUME III. PART I.

Page 165, line 11, *for* "acid," *read* "alkali."
Page 179, footnote, *for* "273°," *read* "283°."
Page 234, line 18 from foot of page, before the word "from," *insert* "free."
Page 341, formula of isodulcite, *for* "$C_6H_2O_5,H_2O$," *read* "$C_6H_{12}O_5,H_2O$."
Pages 378 and 379, in tables, after examining the solution with the tannin reagent, *insert* in each case the instruction :—"The aqueous solution is heated with zinc powder and hydrochloric acid, and filtered rapidly. If the decolorised liquid does not reoxidise on the filter, the filtrate is treated with sodium acetate and then well shaken with air."
Page 398, line 6, after the words "omitted by Hummel," *insert* "whose tables were compiled at a considerably earlier date."
Page 430, under "Toluylene-orange," *for* "page 414," *read* "page 415."

VOLUME III. PART II.

Page 88, line 2, *for* "toluene," *read* "toluylene."
Page 93, line 13, *for* "naphthalene," *read* "naphthylene."
Page 103, line 4, after words "for example," *insert* "0·2 gramme."
Page 106, after word "Piperazine," *insert* "or Piperazidine."
Page 146, line 29, and 147, line 36, *for* "staphysagrine," *read* "staphisagrine."
Page 160, Claus' method of tea-assay is valueless. Compare page 486.
Page 168, in formula of brucine, *for* "H_{29}," *read* "H_{26}."
Page 169, line 11, *for* "quinidine," *read* "quinamine."
Page 169, line 13, *for* "and Remijia barks," *read* "or Remijia bark."
Page 172, line 4 from bottom, *for* "iron," *read* "iodine."
Page 174. For recent information on coniceine, see *Ber.* xxiii. 680; and *Jour, Chem. Soc.*, lviii. 802.
Page 176, lines 8 and 29, *for* "seeds," *read* "fruit."
Page 177, line 13, *for* "128·0," *read* "127·0."
Page 177, line 23, *for* "0·0128," *read* "0·0127."
Page 193. Examination of tobacco-extract, see J. Pinette, *Chem. Zeit.*, xvi. 178; *Analyst.* xvii. 178.
Page 201. See a paper by Dunstan and Umney "On the Alkaloids of the *Aconitum napellus*," *Jour. Chem. Soc.*, lxi. 393.
Pages 244 and 250. O. Hesse has recently shown that hyoscine probably has the formula $C_{17}H_{21}NO_4$, and by saponification yields the base oscine, $C_8H_{13}NO_2$, and not pseudotropine (*Ann. der Chemie*, cclxxi. 100; *Pharm. Jour.*, [3], xxiii. 221).
Page 251. For recent information respecting apoatropine, atropamine belladonnine, and scopolamine, see paper by E. Schmidt and O. Hesse, *Pharm. Jour.*, [3], xxii. 1021; xxiii. 221.
Page 254. For an improved method of separating atropine and hyoscyamine, see O. Hesse, *Pharm. Jour.*, [3], xxiii. 201.
Page 287. For recent researches on benzoyl-pseudotropine, see *Pharm. Jour.*, [3], xxiii. 241.
Page 293. The author is indebted to Mr D. B. Dott for perusal and correction of the section on opium alkaloids.
Page 336, *for* "Meconoïosin," *read* "Meconoïsin."
Page 364. According to D. B. Dott (*Pharm. Jour.*, [3], xxiii. 197), the solubility of strychnine hydrochloride in cold water is 1 in 35.